IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICAL COMPANY LIMITED, a Japanese Corporation, and TAP PHARMACEUTICAL PRODUCTS INC., a Delaware Corporation,	)	
Plaintiffs,	)	
v.	)	C.A. No. _____
BARR PHARMACEUTICALS, INC., a Delaware Corporation, and BARR LABORATORIES, INC., a Delaware Corporation,	)	
Defendants.	)	

COMPLAINT

Plaintiffs Takeda Pharmaceutical Company Limited and TAP Pharmaceutical Products Inc. (collectively, "Plaintiffs"), as and for their Complaint against defendants Barr Pharmaceuticals, Inc. and Barr Laboratories, Inc. ("Defendants"), allege as follows:

THE PARTIES

1. Plaintiff Takeda Pharmaceutical Company Limited ("Takeda") is a Japanese corporation, having a principal place of business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan. As part of its business, Takeda is involved in the research, development, and marketing of pharmaceutical products.

2. Plaintiff TAP Pharmaceutical Products Inc. ("TAP") is a Delaware corporation, having a principal place of business at 675 North Field Drive, Lake Forest, Illinois 60045. As part of its business, TAP is involved in the research, development, and marketing of pharmaceutical products.

3. On information and belief, defendant Barr Pharmaceuticals, Inc. ("Barr Pharmaceuticals") is a Delaware corporation, having a principal place of business located at 400 Chestnut Ridge Road, Woodcliff Lake, NJ 07677 and is engaged in the manufacture and sale of pharmaceutical products.

4. On information and belief, defendant Barr Laboratories, Inc. ("Barr Labs") is a Delaware corporation, having a principal place of business located at Two Quaker Road, P.O. Box 2900, Pomona, NY 10970 and is engaged in the manufacture and sale of pharmaceutical products.

5. On information and belief, Barr Pharmaceuticals owns 100% of the ownership and voting interest in Barr Labs.

6. On information and belief, Barr Labs is controlled and/or dominated by Barr Pharmaceuticals.

7. On information and belief, Barr Pharmaceuticals conducts its North American operations, in part, through Barr Labs.

JURISDICTION AND VENUE

8. This action arises under the patent laws of the United States of America, Title 35, United States Code. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

9. Barr Pharmaceuticals is subject to personal jurisdiction in this District by virtue of, *inter alia*, its incorporation in Delaware, its conduct of business in this District, its purposeful availment of the rights and benefits of Delaware law, and its substantial and continuing contacts with the State.

10. Barr Labs is subject to personal jurisdiction in this District by virtue of, *inter alia*, its incorporation in Delaware, its conduct of business in this District, its purposeful

availment of the rights and benefits of Delaware law, and its substantial and continuing contacts with the State.

11. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391(b), (c) and (d), and 1400(b).

FACTS PERTINENT TO ALL CLAIMS FOR RELIEF

12. On November 7, 1995, the United States Patent & Trademark Office ("PTO") issued U.S. Patent No. 5,464,632 ("the '632 Patent"), entitled "Rapidly Disintegratable Multiparticular Tablet," to Laboratoires Prographarm, the assignee of the named inventors Gerard Cousin, Etienne Bruna, and Edouard Gendrot. Laboratoires Prographarm granted Plaintiff Takeda an exclusive license to the '632 Patent in the field of proton pump inhibitors with the right to sublicense. Ethypharm subsequently acquired Laboratoires Prographarm and is the record owner of the '632 Patent. Plaintiff TAP is the exclusive sublicensee to the '632 Patent. On February 20, 2001, the PTO issued a Reexamination Certificate for the '632 Patent. A copy of the '632 Patent and its Reexamination Certificate is attached hereto as Exhibit A.

13. On December 11, 2001, the PTO issued U.S. Patent No. 6,328,994 ("the '994 Patent"), entitled "Orally Disintegrating Tablets," to Takeda Chemical Industries, Ltd. (now Takeda Pharmaceutical Company Limited), the assignee of the named inventors Toshihiro Shimizu, Shuji Morimoto, and Tetsuro Tabata. Plaintiff Takeda is the record owner of the '994 Patent, and Plaintiff TAP is the exclusive licensee. A copy of the '994 Patent is attached hereto as Exhibit B.

14. On August 30, 2002, the United States Food and Drug Administration ("FDA") approved New Drug Application ("NDA") No. 21-428 for lansoprazole delayed release orally disintegrating tablets, 15 and 30 mg. TAP is the holder of NDA No. 21-428 for

lansoprazole delayed release orally disintegrating tablets, which it sells under the name Prevacid® SoluTab™.

15. The ’632 and ’994 Patents (collectively, “the patents-in-suit”) are listed in a publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as the “Orange Book”) as covering Prevacid® SoluTab™, delayed release orally disintegrating tablets, 15 and 30 mg.

16. On information and belief, through the coordinated efforts of research and development staff at least in North America, Barr Pharmaceuticals seeks to constantly expand the range of generic products it sells.

17. On information and belief, Defendants collaborate in the manufacture, marketing, and sale of many pharmaceutical products (including generic drug products manufactured and sold pursuant to an approved abbreviated new drug application) within the United States generally and the State of Delaware specifically.

18. On information and belief, Defendants actively review pharmaceutical patents and seek opportunities to challenge those patents.

19. On information and belief, Defendants reviewed the patents-in-suit and certain commercial and economic information relating to Prevacid® SoluTab™, including estimates of the revenues generated by the sale of Prevacid® SoluTab™, and decided to file an Abbreviated New Drug Application (“ANDA”), seeking approval to market lansoprazole delayed release orally disintegrating tablets.

20. On information and belief, Defendants collaborated in the research, development, preparation and filing of Abbreviated New Drug Application (“ANDA”) No. 90-152 for lansoprazole delayed release orally disintegrating tablets.

21. On information and belief, Barr Labs submitted to the FDA ANDA No. 90-152 to seek approval to engage in the commercial manufacture, use and sale of lansoprazole delayed-release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the patents-in-suit.

22. Plaintiffs have received a letter dated April 24, 2008, from Barr Labs notifying them that Barr Labs's ANDA No. 90-152 includes a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV certification") that, in Barr Labs's opinion, the patents-in-suit are invalid, unenforceable or will not be infringed by the commercial manufacture, use or sale of the lansoprazole delayed release orally disintegrating tablet products described in ANDA No. 90-152.

23. On information and belief, Barr Pharmaceuticals made the ultimate decision to file ANDA No. 90-152 with the FDA, and knowingly encouraged, directed and actively induced Barr Labs to file ANDA No. 90-152 and Paragraph IV certification, and Barr Labs did so at Barr Pharmaceuticals' direction.

24. On information and belief, Barr Pharmaceuticals was necessarily aware of the patents-in-suit when it directed Barr Labs to file ANDA No. 90-152 and a Paragraph IV certification.

25. Plaintiffs commenced this action within 45 days of the date they received Barr Labs's notice of ANDA No. 90-152 containing the Paragraph IV certification.

26. On information and belief, Defendants continue to collaborate in seeking approval of ANDA No. 90-152 from the FDA and intend to collaborate in the commercial manufacture, marketing and sale of lansoprazole delayed release orally disintegrating tablets

(including commercial marketing and sale of such products in the State of Delaware) in the event that FDA approves ANDA No. 90-152.

FIRST CLAIM FOR RELIEF
(Direct Infringement of the '632 Patent by Barr Labs and Barr Pharmaceuticals)

27. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 26 hereof, as if fully set forth herein.

28. Through the conduct alleged above, Defendants have directly infringed, and continue to directly infringe, one or more claims of the '632 Patent.

29. By filing ANDA No. 90-152 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the '632 Patent, Defendants have infringed the '632 Patent under 35 U.S.C. § 271(e)(2).

30. Defendants were aware of the existence of the '632 Patent prior to filing ANDA No. 90-152 but took such action knowing that it would constitute an infringement of the '632 Patent.

31. On information and belief, Defendants acted without a reasonable basis for a good faith belief that they would not be liable for infringing the '632 Patent.

32. Defendants' conduct renders this case "exceptional" as described in 35 U.S.C. § 285.

33. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the '632 Patent.

SECOND CLAIM FOR RELIEF
(Inducement of Infringement of the '632 Patent by Barr Pharmaceuticals)

34. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 33 hereof, as if fully set forth herein.

35. Through the conduct alleged above, Barr Pharmaceuticals has knowingly and actively induced Barr Labs to infringe, and continue to infringe, one or more claims of the '632 Patent.

36. By reason of Barr Pharmaceuticals' inducement of Barr Labs's direct infringement of the '632 Patent, Barr Pharmaceuticals has caused and continues to cause irreparable harm to Plaintiffs.

37. On information and belief, Barr Pharmaceuticals' inducement of Barr Labs's direct infringement of the '632 Patent will continue unless enjoined by this Court.

38. Plaintiffs have no adequate remedy at law for Barr Pharmaceuticals' inducement of Barr Labs's direct infringement of the '632 Patent.

39. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorney fees.

THIRD CLAIM FOR RELIEF
(Direct Infringement of the '994 Patent by Barr Labs and Barr Pharmaceuticals)

40. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 39 hereof, as if fully set forth herein.

41. Through the conduct alleged above, Defendants have directly infringed, and continue to directly infringe, one or more claims of the '994 Patent.

42. By filing ANDA No. 90-152 with a Paragraph IV certification seeking FDA approval to engage in the commercial manufacture, use and sale of lansoprazole delayed release orally disintegrating tablets, 15 and 30 mg, prior to the expiration of the '994 Patent, Defendants have infringed the '994 Patent under 35 U.S.C. § 271(e)(2).

43. Defendants were aware of the existence of the ’994 Patent prior to filing ANDA No. 90-152 but took such action knowing that it would constitute an infringement of the ’994 Patent.

44. On information and belief, Defendants acted without a reasonable basis for a good faith belief that they would not be liable for infringing the ’994 Patent.

45. Defendants’ conduct renders this case “exceptional” as described in 35 U.S.C. § 285.

46. Plaintiffs will be irreparably harmed if Defendants are not enjoined from infringing the ’994 Patent.

FOURTH CLAIM FOR RELIEF
(Inducement of Infringement of the ’994 Patent by Barr Pharmaceuticals)

47. Plaintiffs repeat and reallege each and every allegation contained in paragraphs 1 through 46 hereof, as if fully set forth herein.

48. Through the conduct alleged above, Barr Pharmaceuticals has knowingly and actively induced Barr Labs to infringe, and continue to infringe, one or more claims of the ’994 Patent.

49. By reason of Barr Pharmaceuticals’ inducement of Barr Labs’s direct infringement of the ’994 Patent, Barr Pharmaceuticals has caused and continues to cause irreparable harm to Plaintiffs.

50. On information and belief, Barr Pharmaceuticals’ inducement of Barr Labs’s direct infringement of the ’994 Patent will continue unless enjoined by this Court.

51. Plaintiffs have no adequate remedy at law for Barr Pharmaceuticals’ inducement of Barr Labs’s direct infringement of the ’994 Patent.

52. This is an exceptional case within the meaning of 35 U.S.C. § 285, which warrants reimbursement of Plaintiffs' reasonable attorneys' fees.

WHEREFORE, Plaintiffs respectfully request the following relief:

A. An order adjudging and decreeing that Defendants have infringed the patents-in-suit;

B. An order adjudging and decreeing that Barr Pharmaceuticals has induced infringement of the patents-in-suit;

C. An order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of ANDA No. 90-152 be no earlier than the expiration date of the last of the patents-in-suit, including any extensions;

D. A preliminary and permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) restraining and enjoining Barr Labs and Barr Pharmaceuticals, their officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the lansoprazole products described in ANDA No. 90-152 or any other ANDA not colorably different from ANDA No. 90-152 until the expiration date of the last of the patents-in-suit, including any extensions;

E. A declaration that this case is exceptional and an award of attorneys' fees under 35 U.S.C. § 285 and costs and expenses in this action; and

F. Such other and further relief as the Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Rodger D. Smith II

Jack B. Blumenfeld (#1014)
Mary B. Graham (#2256)
Rodger D. Smith II (#3778)
James W. Parrett, Jr. (#4292)
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19899-1347
(302) 658-9200
rsmith@mnat.com
Attorneys for Takeda Pharmaceutical Company Limited and TAP Pharmaceutical Products Inc.

OF COUNSEL:

Eric J. Lobenfeld
Tedd W. Van Buskirk
Arlene L. Chow
Dillon Kim
HOGAN & HARTSON LLP
875 Third Avenue
New York, NY 10022
(212) 918-3000

Philippe Y. Riesen
HOGAN & HARTSON LLP
Shinjuku Center Building, 46th Floor
25-1 Nishi-Shinjuku 1-chome
Shinjuku, Tokyo 163-0646
Japan
(81) 3-5908-4070

Attorneys for *Takeda Pharmaceutical Company Limited*

William F. Cavanaugh
Stuart E. Pollack
Chad J. Peterman
Patrick S. Almonrode
PATTERSON BELKNAP WEBB & TYLER LLP
1133 Avenue of the Americas
New York, NY 10036
(212) 336-2000

Attorneys for TAP Pharmaceutical Products Inc.

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2356622

EXHIBIT A

US005464632A

United States Patent [19]

Cousin et al.

[11] **Patent Number: 5,464,632**

[45] **Date of Patent: Nov. 7, 1995**

[54] **RAPIDLY DISINTEGRATABLE MULTIPARTICULAR TABLET**

[75] Inventors: **Gérard Cousin**, Gallardon; **Etienne Bruna**, Chartres; **Edouard Gendrot**, Vernouillet, all of France

[73] Assignee: **Laboratoires Prographarm**, Chateauneuf, France

[21] Appl. No.: **346,324**

[22] Filed: **Nov. 29, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 35,355, Mar. 22, 1993, abandoned.

[30] **Foreign Application Priority Data**

Jul. 22, 1991 [FR] France 91 09245

[51] **Int. Cl.**[6] **A61K 9/20**

[52] **U.S. Cl.** **424/465**; 424/458; 424/489

[58] **Field of Search** 424/458, 440, 424/465, 428, 441, 473, 489

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,915,953	4/1990	Jordan et al.	424/473
5,073,374	12/1991	McCarty	424/465
5,073,377	12/1991	Alexander et al.	424/465
5,215,756	6/1993	Gole et al.	424/441

FOREIGN PATENT DOCUMENTS

0255002	7/1987	European Pat. Off. .
0281200	2/1988	European Pat. Off. .
0408273	7/1990	European Pat. Off. .

Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.

[57] **ABSTRACT**

Rapidly disintegratable multiparticulate tablet the excipient mixture of which is suitable for imparting a disintegration rate such that the tablet disintegrates in the mouth in an extremely short time, notably in less than sixty seconds, characterized by the fact that the active substance is present in the form of coated microcrystals or coated or uncoated microgranules.

6 Claims, No Drawings

RAPIDLY DISINTEGRATABLE MULTIPARTICULAR TABLET

This application is a continuation of application Ser. No. 08/035,355, filed Mar. 22, 1993, abandoned.

The invention relates to a rapidly disintegratable multiparticulate tablet, i.e. a pharmaceutical presentation for oral administration whose disintegration rate is such that, when it is placed into the buccal cavity and particularly on the tongue, it disintegrates in less than sixty seconds providing with the saliva present a suspension easy to be swallowed.

The disintegration rate is obtained due to a mixture of excipients or vehicles which comprises generally a disintegrating agent which may consist of a carboxymethylcellulose and a swelling agent which may consist of modified starch.

The active substance or principle is mixed with the abovesaid vehicles, the mixture then being tabletted after addition of a lubricant such as, for example, magnesium stearate.

The Applicants have had the merit of having found that it was possible, unexpectedly and surprisingly, to introduce into a multiparticulate tablet with high disintegration rate such as hereabove defined, the active substance in the form of coated or non-coated microcrystals or microgranules; thus, the physician has at his disposal a rapidly disintegratable multiparticulate tablet proper to facilitate the taking by the patient of most diversified active substances and especially of those whose taste is particularly unpleasant, the said tablet permitting the taking of the said active substances with as diversified features as gastroresistance and controlled release due to the fact that the said coated or non-coated microcrystals and microgranules preserve, after having been shaped in the form of a multiparticulate tablet, their initial properties amongst which masking of taste, gastroresistance and controlled release of the active principle.

Consequently, the rapidly disintegratable multiparticulate tablet according to the invention, which can be used for human beings and for animals, the excipient mixture of which is such as to provide it with a disintegration rate so that its disintegration in the buccal cavity occurs in an extremely short time and especially shorter than sixty seconds, is characterized by the fact that the active substance is in the form of coated or non-coated microcrystals or microgranules with modified action or non-modified action.

According to an advantageous embodiment of the abovesaid tablet, the mixture of excipients comprises one or several disintegrating agents of the carboxymethylcellulose type or insoluble reticulated PVP type, one or several swelling agents which may consist of a carboxymethylcellulose, a starch, a modified starch, for instance a carboxymethylated starch, or a microcrystalline cellulose, and possibly a direct compression sugar consisting for example of 92% of dextrose.

According to an advantageous embodiment, the tablets according to the invention, wherein the active substance is in the form of coated microcrystals, comprise as active substance at least one of those of the group comprising the gastrointestinal sedatives, the antacids, the analgesics, the anti-inflammatory agents, the coronary vasodilators, the peripheral and brain-vasodilators, the anti-infectious agents, the antibiotics, the antiviral agents, the antiparasitic agents, the anticancerous drugs, the antianxiety agents, the neuroleptic drugs, the agents stimulating the central nervous system, the antidepressant drugs, the antihistaminic agents, the antidiarrheal agents, the laxatives, the nutritional supplements, the immunodepressant drugs, the cholesterol lowering agents, the hormones, the enzymes, the antispasmodic agents, the antiangorous agents, the drugs acting on the rhythm of the heart, the drugs used in the treatment of arterial hypertension, the anti-migraine agents, the drugs acting on blood coagulability, the antiepileptic agents, the myorelaxing agents, the drugs used in the treatment of diabetes, the drugs used in the treatment of thyroidal dysfunctions, the diuretical agents, the anorexigenic drugs, the antiasthmatic agents, the expectorants, the antitussive agents, the mucoregulators, the decongestants, the hypnotics, the antinauseous agents, the hematopoietical agents, the uricosuric agents, the plant extracts, the contrast mediums.

According to another advantageous embodiment, the tablets according to the invention, wherein the active substance is present in the form of coated or non-coated microgranules with modified action or non-modified action, comprise as active substance at least one of those of the group comprising the gastrointestinal sedatives, the antacids, the analgesics, the anti-inflammatory agents, the coronary vasodilators, the peripheral and brain-vasodilators, the anti-infectious agents, the antibiotics, the antiviral agents, the antiparasitic agents, the anticancerous drugs, the antianxiety agents, the neuroleptic drugs, the agents stimulating the central nervous system, the antidepressant drugs, the antihistaminic agents, the antidiarrheal agents, the laxatives, the nutritional supplements, the immunodepressant drugs, the cholesterol lowering agents, the hormones, the enzymes, the antispasmodic agents, the antiangorous agents, the drugs acting on the rhythm of the heart, the drugs used in the treatment of arterial hypertension, the anti-migraine agents, the drugs acting on blood coagulability, the antiepileptic agents, the myorelaxing agents, the drugs used in the treatment of diabetes, the drugs used in the treatment of thyroidal dysfunctions, the diuretical agents, the anorexigenic drugs, the antiasthmatic agents, the expectorants, the antitussive agents, the mucoregulators, the decongestants, the hypnotics, the antinauseous agents, the hematopoietical agents, the uricosuric agents, the plant extracts, the contrast mediums.

The use of the tablet according to the invention is especially advantageous due to the fact that it may be very easily used by any users. The said tablet can be taken in any condition (when working, when travelling and so on), without a glass and without water. It constitutes an "ambulatory" pharmaceutical presentation which can advantageously be used instead of numerous pharmaceutical presentations such as sachets, effervescent tablets, drinkable ampoules, capsules, traditional tablets and so on.

Its very easy facility of administration is especially interesting when it is necessary that young children or old people take therapeutical substances, i.e. populations which often have swallowing difficulties, i.e. populations which keep the drug in the mouth and which are unable to swallow it. Contrary to the traditional tablet or to the capsule, the tablet according to the invention offers in connection with such populations an advantage of security as, as soon as it is introduced in the mouth, it provides a therapeutical protection.

On the other hand, it is important to emphasize that, even directly swallowed with a little water for example, the said tablet preserves its rapid disintegration rate within the stomach. This type of administration will again raise no security problem.

Furthermore, the tablet according to the invention provides a further big advantage with respect to tablets or simple capsules. In fact until today, people who need to swallow a tablet or a capsule under the above-mentioned

conditions (during working, during travelling, without water and without a glass), swallowed the said tablet or capsule without water and that could be dangerous as the tablet or capsule can block in the esophagus and provide thus an important delay as far as absorption of the active principle is concerned or even an ulceration at the level of the esophagus. Similarly, the fact that, on the one hand, the active principle is coated and, on the other hand, that it is present in the form of a multiparticulate tablet, prevents agressive active principles causing ulcerations of the esophagial or gastric mucous membranes, phenomenon which is sometimes caused by certain pharmaceutical presentations which are monolithic, especially when the patient suceeeds in swallowing them with a little water or no water.

Another advantage of the tablet according to the invention is that the said tablet has not the well-known drawbacks of effervescent tablets as for instance the taste which is very unpleasant to the child, the high sodium content which is disturbing to people which must follow a diet without sodium and finally the necessity of having water and a glass for its administration.

Furthermore, it permits the formulation of certain active principles which are not adapted to a previous extracorporeal dissolution and which consequently can be contemplated only under a dry form, which prevents their use in effervescent tablets; consequently, the tablet according to the present invention has all the advantages of the dry forms, i.e. the stability as well as the facility of packaging and storage.

On the other hand, this new pharmaceutical form may contain if necessary two or several active principles which are usually incompatible with one another and this without alteration of their stability.

Another advantage of the tablet according to the invention consists in the possibility of taking by the patient of doses of active principle which are more important than in the past. As a matter of fact as the said tablet is not to be swallowed under its initial form but after disintegration within the buccal cavity, its size might be greater than that of a classical pharmaceutical form which must be adapted to be swallowed without disturbing the taking of the drug.

Finally, the tablet according to the invention has all the advantages of coated particles which permit to obtain especially a taste-masking, a gastroresistance, a delayed release as well as all the advantages of the multiparticulate forms with modified action or non-modified action, i.e. a great exchange surface, the dispersion, less inter- and intra-individual variations, a very reduced gastric empting influence, a very reduced intestinal transit time influence as well as reduced pH influence in the digestive tract, reduced influence of the viscosity and consequently of food and of the position of the body, without local toxic manifestation.

The preparation of the rapidly disintegratable multiparticulate tablets according to the invention is as follows or similar.

When the active principle is in the form of coated microcrystals, it is possible to proceed as follows.

The microcrystals are coated by way of a process known by itself such as, for example, the fluidized air bed, the coacervation and the microencapsulation.

The mixture of excipients is then prepared by the dry- or wet-granulation method.

Then, the coated microcrystals are mixed under dry conditions with the mixture of excipients before compression.

The preparation of the tablet according to the invention wherein the active principle is in the form of coated or non-coated microgranules, may be as follows.

The active principle is put in the form of microgranules by way of a method known by itself such as, for example, extrusion-spheronisation, manufacture in pan, fluidized air bed and so on.

Once obtained, these microgranules are coated if necessary in a pan or in a fluidized air bed.

The mixture of excipients is then prepared by the dry- or wet-granulation method.

Then, the coated or non-coated microgranules are mixed under dry conditions with the mixture of excipients before compression.

The invention may even be better understood by way of the following non-limitating examples which relate to advantageous embodiments of the invention.

EXAMPLE 1

Rapidly disintegratable multiparticulate tablet based on coated crystals of paracetamol.

Tablets according to the invention are prepared whose composition is as follows.

Formula:	
coated paracetamol (with 6% ethylcellulose)	530 mg
direct compression sugar	160 mg
microcrystalline cellulose	90 mg
reticulated polyvinylpyrrolidone	60 mg
sodic carboxymethylcellulose	50 mg
colloidal silica	6 mg
lubricant	4 mg
sweetener	25 mg
aroma	15 mg
magnesium trisilicate	50 mg
Total	990 mg

The said tablet is prepared as follows.

The paracetamol crystals are introduced in a fluidized air bed installation and a solution of ethylcellulose in an ethanol/acetone mixture is sprayed thereon.

The excipients are sieved and the coated paracetamol is homogeneized with the excipients inside a mixing device under dry conditions.

Distribution and tabletting are carried out on a compressing machine fitted with punches having a diameter equal to 15 mm and a radius of curvature equal to 20 mm.

The pressure is equal to 16 KNewtons ±1. The hardness of the thus obtained tablets is equal to 100 Newtons ±10. The time of disintegration in the mouth is from 35 to 45 seconds.

EXAMPLE 2

Rapidly disintegratable multiparticulate tablet based on coated cimetidine crystals.

Tablets according to the invention are prepared whose composition is as follows.

Formula:	
coated cimetidine (with 15.25% of Eudragit E)	944 mg
reticulated polyvinylpyrrolidone	89 mg
magnesium stearate	5 mg
sweetener	50 mg
aroma	12 mg
Total	1100 mg

The said tablet is prepared as follows.

The cimetidine crystals are introduced in a fluidized air bed installation and a solution of a copolymer of dimethylaminoethyl-methacrylate and of neutral esters of methacrylic acid known under the trademark "Eudragit E" in alcohol is sprayed thereon.

The excipients are sieved and the coated cimetidine is homogeneized with the excipients inside a mixing apparatus under dry conditions.

Distribution and tabletting are executed on a compressing machine equipped with punches having a diameter equal to 16 mm and a radius of curvature equal to 20 mm.

The pressure is 20 KNewtons ±1. The hardness of the thus obtained tablets is 95 Newtons ±10. The time of disintegration in the mouth is from 15 to 20 seconds.

EXAMPLE 3

Rapidly disintegratable multiparticulate tablet based on coated crystals of paracetamol.

Tablets according to the invention composed as follows are prepared.

Formula:	
complex of paracetamol-codeine (30 mg of codeine and 18.4% of Eudragit*)	627.5 mg
reticulated polyvinylpyrrolidone	90 mg
sodium carboxymethylcellulose	70 mg
starch commercialized under the trademark "STARCH 1500"	100 mg
sweetener	40 mg
aroma	22.5 mg
Total	950 mg

*Eudragit is a copolymer of methacrylic acid.

This tablet is prepared as follows.

The crystals of paracetamol are introduced in a fluidized air bed installation and the codeine dissolved in a solution of Eudragit E and Eudragit NE 30D (neutral polymer of esters of polymethacrylic acid) is sprayed thereon.

The excipients are sieved and the coated paracetamol is homogeneized with the excipients in a mixing apparatus under dry conditions.

Distribution and tabletting are carried out on a compressing machine equipped with punches having a diameter equal to 16 mm and a radius of curvature equal to 20 mm.

The pressure is 21 KNewtons ±1. The hardness of the thus obtained tablets is 35 Newtons ±5. The time of disintegration in the mouth is from 50 to 60 seconds.

EXAMPLE 4

Rapidly disintegratable multiparticulate tablet based on coated crystals of ibuprofen.

Tablets according to the invention and whose composition is as follows are prepared.

Formula:	
ibuprofen (with 10% of ethylcellulose)	440 mg
reticulated polyvinylpyrrolidone	120 mg
starch commercialized under the trademark "STARCH 1500"	235 mg
sweetener	48 mg
aroma	52 mg
magnesium stearate	5 mg
Total	900 mg

This tablet is prepared as follows.

The crystals of ibuprofen are introduced in a fluidized air bed installation and a solution of ethylcellulose in ethanol is sprayed thereon.

The excipients are sieved and the coated ibuprofen is homogeneized with the excipients in a mixing apparatus under dry conditions.

Distribution and tabletting are carried out on a compressing machine equipped with punches having a diameter equal to 16 mm and a radius of curvature equal to 20 mm.

The pressure is 15 KNewtons ±1. The hardness of the thus obtained tablets is 50 Newtons ±5. The time of disintegration in the mouth is from 15 to 20 seconds.

EXAMPLE 5

Rapidly disintegratable multiparticulate tablet based on microgranules.

Formula:	
microgranules with delayed release based on doxycycline monohydrate (with 100 mg of active principle)	225 mg
microcrystalline cellulose	142 mg
starch commercialized under the trademark "SEPPISTAB ST 500"	98 mg
aspartam	20 mg
aroma	15 mg
Total	500 mg

The microgranules are prepared in a pan by coating a neutral sugar sphere with doxycycline according to the classical technology, the microgranules being then coated with Eudragit E also in coating pan.

The tablet is prepared by sieving of the excipients, followed by homogeneization of the microgranules of doxycycline with the excipients in a mixing apparatus under dry conditions, followed by distribution and tabletting in a rotary compressing machine equipped with punches having a diameter equal to 12 mm and radius of curvature is equal to 11 mm.

The pressure is 20 KNewtons ±1. The hardness of the thus obtained tablets is 100 Newtons ±10. The time of disintegration in the mouth is from 10 to 20 seconds.

As a result of which we have a rapidly disintegratable multiparticulate tablet, the constitution and method of manufacture of which are sufficiently disclosed above, such that it would be useless to repeat this subject and about which it is recalled that

- it consists of a tablet which combines a high level technology (control of release, of gastroresistance, of taste-masking of the active principle) with a high security of use due to its multiparticulate form by way of the coating during the process of manufacture and to the fact that its disintegration occurs in the mouth,
- it constitutes an ambulatory form which can be adapted to a great number of active principles and to high dosages, which did not previously exist,
- it offers a high facility of use, as the same pharmaceutical form can be disintegrated within the mouth, in a glass of water or in liquid or semi-liquid food, as for example, in yoghourt for children or infants, or in food for animals in connection with its use in the veterinary field,
- it consists of a single and same pharmaceutical form which can be prescribed to people requiring different strengths; thus, it can be used in connection with an active principle given at its maximum dose and manufactured in a divisible shape at one or several scored places in such a manner that it can be administered in totality or according to the age or the symptoms of the patient, in the form of a divisible part depending upon the shape of the punch, it being emphasized that it was not obvious to obtain a divisible multiparticulate tablet,
- it consequently consists of a pharmaceutical form which is suitable to everybody because it offers a great variety of means for administration and of dosages, which represents a definite economical advantage.

The fact that a single product permits, on the one hand, ways of administration normally permitted by several pharmaceutical forms and that, on the other hand, it gives rise to several posologies normally obtained by the creation of various strengths (tablets or capsules of different concentrations for example) constitutes an economical advantage of primary importance.

In fact from the industrial point of view, this means a single line production instead of several lines production each corresponding to each strength selected and to each pharmaceutical form selected.

We claim:

1. A rapidly disintegratable tablet for oral administration with or without the use of water, said tablet comprising an active substance and a mixture of excipients, wherein said active substance is multiparticulate and in the form of coated microcrystals, coated microgranules or uncoated microgranules and wherein said mixture of excipients comprises excipients which are responsible for the disintegration, said tablet being intended to be swallowed said disintegration occurring in less than sixty seconds under the action of the excipients which are responsible for the disintegration and which are selected from the group consisting at least one disintegrating agent and at least one swelling agent.

2. The tablet of claim **1**, wherein the active substance is in the form of coated microcrystals and is selected from the group consisting of gastrointestinal sedatives, antacids, analgesics, anti-inflammatory agents, coronary vasodilators, peripheral and brain-vasodilators, anti-infectious agents, antibiotics, antiviral agents, antiparasitic agents, anticancerous drugs, antianxiety agents, neuroleptic drugs, agents stimulating the central nervous systems, antidepressant drugs, antihistaminic agents, antidiarrheal agents, laxatives, nutritional supplements, immunodepressant drugs, cholesterol lowering agents, hormones, enzymes, antispasmodic agents, antiangorous agents, drugs acting on the rhythm of the heart, drugs used in the treatment of arterial hypertension, anti-migraine agents, drugs acting on blood coagulability, anti-epileptic agents, myorelaxing agents, drugs used in the treatment diabetes, drugs used in the treatment of thyroidal dysfunctions, diuretical agents, anorexigenic drugs, anti-asthmatic agents, expectorants, antitussive agents, mucoregulators, decongestants, hypnotics, antinausea agents, hematopoietical agents, uricosuric agents, plant extracts and contrast mediums.

3. The tablet of claim **1**, wherein the active substance is in the form of coated microgranules and is selected from the group consisting of gastrointestinal sedatives, antacids, analgesics, anti-inflammatory agents, coronary vasodilators, peripheral and brain-vasodilators, anti-infectious agents, antibiotics, antiviral agents, antiparasitic agents, anticancerous drugs, antianxiety agents, neuroleptic drugs, agents stimulating the central nervous system, anti-depressant drugs, antihistaminic agents, antidiarrheal agents, laxatives, nutritional supplements, immunodepressant drugs, cholesterol lowering agents, hormones, enzymes, anti-spasmodic agents, antiangorous agents, drugs acting on the rhythm of the heart, drugs used in the treatment of arterial hypertension, anti-migraine agents, drugs acting on blood coagulability, anti-epileptic agents, myorelaxing agents, drugs used in the treatment of diabetes, drugs used in the treatment of thyroidal dysfunctions, diuretical agents, anorexigenic drugs, anti-asthmatic agents, expectorants, antitussive agents, mucoregulators, decongestants, hypnotics, antinausea agents, hematopoietical agents, uricosuric agents, plant extracts and contrast mediums.

4. The tablet of claim **1**, wherein the mixture of excipients comprises at least one disintegrating agent selected from the group consisting of carboxymethylcellulose, insoluble reticulated PVP type and at lest one swelling agent selected from the group consisting of starch, modified starch and microcrystalline cellulose.

5. The tablet of claim **1**, wherein the mixture of excipients comprises at least one disintegrating agent selected from the group consisting of carboxymethylcellulose and insoluble reticulated PVP, and at least one swelling agent selected from the group consisting of starch, modified starch and microcrystalline cellulose and a direct compression sugar.

6. The tablet of claim **1**, wherein the active substance is in the form of uncoated microgranules and is selected from the group consisting of gastrointestinal sedatives, antacids, analgesics, anti-inflammatory agents, coronary vasodilators, peripheral and brain-vasodilators, anti-infectious agents, antibiotics, antiviral agents, antiparasitic agents, anticancerous drugs, antianxiety agents neuroleptic drugs, agents stimulating the central nervous system anti-depressant drugs antihistaminic agents, antidiarrheal agents, laxatives, nutritional supplements, immunodepressant drugs, cholesterol lowering agents, hormones, enzymes, anti-spasmodic agents, antiangorous agents, drugs acting on the rhythm of the heart, drugs used in the treatment of arterial hypertension, anti-migraine agents, drugs acting on blood coagulability, anti-epileptic agents, myorelaxing agents, drugs used in the treatment of diabetes, drugs used in the treatment of thyroidal dysfunctions, diuretical agents, anorexigenic drugs, anti-asthmatic agents, expectorants, antitussive agents, mucoregulators, decongestants, hypnotics, anti-nausea agents, hematopoietical agents, uricosuric agents, plant extracts and contrast mediums.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,464,632

DATED : November 7,1995

INVENTOR(S) : Gerard Cousin et al

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 7, claim 1, line 61, add "of" after consisting.

Signed and Sealed this

Seventh Day of January, 1997

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

US005464632C1

(12) REEXAMINATION CERTIFICATE (4273rd)

United States Patent

Cousin et al.

(10) Number: US 5,464,632 C1

(45) Certificate Issued: Feb. 20, 2001

(54) **RAPIDLY DISINTEGRATABLE MULTIPARTICULAR TABLET**

(75) Inventors: **Gérard Cousin**, Gallardon; **Etienne Bruna**, Chartres; **Edouard Gendrot**, Vernouillet, all of (FR)

(73) Assignee: **Laboratoires Prographarm**, Chateaueuf-en-Thymerals (FR)

Reexamination Request:
No. 90/005,207, Dec. 31, 1999

Reexamination Certificate for:

Patent No.:	**5,464,632**
Issued:	**Nov. 7, 1995**
Appl. No.:	**08/346,324**
Filed:	**Nov. 29, 1994**

Certificate of Correction issued Dec. 12, 1996.

Related U.S. Application Data

(63) Continuation of application No. 08/035,355, filed on Mar. 22, 1993, now abandoned.

(30) **Foreign Application Priority Data**

Jul. 22, 1991 (FR) 91 09245

(51) **Int. Cl.**[7] **A61K 9/20**

(52) **U.S. Cl.** **424/465**; 424/489; 424/490; 424/495; 424/497

(58) **Field of Search** 424/465, 489, 424/490, 495, 497

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(List continued on next page.)

Primary Examiner—Thurman K. Page

(57) **ABSTRACT**

Rapidly disintegratable multiparticulate tablet the excipient mixture of which is suitable for imparting a disintegration rate such that the tablet disintegrates in the mouth in an extremely short time, notably in less than sixty seconds, characterized by the fact that the active substance is present in the form of coated microcrystals or coated or uncoated microgranules.

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REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claim **6** is cancelled.

Claims **1** and **4** are determined to be patentable as amended.

Claims **2**, **3**, **5**, dependent on an amended claim, are determined to be patentable.

1. A rapidly disintegratable tablet for oral administration [with or] *and disintegration in the buccal cavity* without the use of water, *wherein* said tablet [comprising] *comprises* an active substance and a mixture of *non-effervescent* excipients [wherein said active substance is] *and permits to obtain reduced ph influence in the digestive tract and reduced influence of viscosity, said active substance being* multiparticulate and in the form of coated microcrystals, *or* coated microgranules [or uncoated microgranules] and wherein said mixture of excipients comprises [excipients which are responsible for the disintegration, said tablet being intended to be swallowed said disintegration occurring in less than sixty seconds under the action of the excipients which are responsible for the disintegration and which are selected from the group consisting at least one] *a* disintegrating agent and [at least one] swelling agent *which are responsible for the disintegration of the tablet with the saliva present in the mouth, to achieve in less than 60 seconds a suspension easy to swallow.*

4. The tablet of claim **1**, wherein the mixture of excipients comprises at least one disintegrating agent selected from the group consisting of carboxymethylcellulose, insoluble reticulated PVP [type] and at [lest] *least* one swelling agent selected from the group consisting of starch, modified starch and microcrystalline cellulose.

* * * * *

EXHIBIT B

US006328994B1

(12) **United States Patent**
Shimizu et al.

(10) **Patent No.: US 6,328,994 B1**
(45) **Date of Patent: Dec. 11, 2001**

(54) **ORALLY DISINTEGRABLE TABLETS**

(75) Inventors: **Toshihiro Shimizu**, Itami; **Shuji Morimoto**; **Tetsuro Tabata**, both of Suita, all of (JP)

(73) Assignee: **Takeda Chemical Industries, Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/355,781**

(22) PCT Filed: **May 17, 1999**

(86) PCT No.: **PCT/JP99/02548**

§ 371 Date: **Aug. 4, 1999**

§ 102(e) Date: **Aug. 4, 1999**

(87) PCT Pub. No.: **WO99/59544**

PCT Pub. Date: **Nov. 25, 1999**

(30) **Foreign Application Priority Data**

May 18, 1998 (JP) 10-135472
Aug. 3, 1998 (JP) 10-219266
Aug. 5, 1998 (JP) 10-222151
Oct. 29, 1998 (JP) 10-344810
Jan. 12, 1999 (JP) 11-005144
Jan. 25, 1999 (JP) 11-015851

(51) **Int. Cl.**[7] **A61K 9/14**; A61K 9/20; A61K 9/46; A61K 9/16

(52) **U.S. Cl.** **424/489**; 424/464; 424/465; 424/466; 424/490; 424/493

(58) **Field of Search** 424/464, 465, 424/466, 489, 490, 493

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Primary Examiner—Thurman K. Page
Assistant Examiner—S. Tran
(74) *Attorney, Agent, or Firm*—Mark Chao; Elaine M. Ramesh

(57) **ABSTRACT**

An orally disintegrable tablet, of the present invention, which comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive, has superior disintegrability or dissolution in the oral cavity so that it can be used for treatment or prevention of various diseases, as an orally disintegrable tablet capable of being administered to the aged or children and easily administered without water. Also, because the tablet of the present invention contains fine granules having the average particle diameter such that it will not impart roughness in mouth, it can be administered easily without discomfort at the administration.

45 Claims, No Drawings

ORALLY DISINTEGRABLE TABLETS

This application is a 371 of PCT/JP99/02548 filed May 17, 1999.

This application is the National Stage of International Application Serial No. PCT/JP99/02548, filed May 17, 1999.

TECHNICAL FIELD

The present invention relates to an orally disintegrable tablet having a characteristic of fast disintegration in the oral cavity even without water.

BACKGROUND ART

Pharmaceutical solid preparations, for example, tablets, usually are prepared to make pharmaceutically active ingredients absorb in a digestive organ by disintegration or dissolution through oral administration, without fast disintegration or dissolution in the Qral cavityl

JP-A-6-502194 (U.S. Pat. No. 5,464,632) discloses a rapidly disintegrable multiparticulate tablet, the excipient mixture of which is suitable for imparting a disintegration rate such that the tablet disintegrates in the mouth in less than sixty seconds, characterized by the fact that the active substance is present in the form of coated microcrystals or coated or uncoated microgranules. However, there is no disclosure of an acid-labile physiologically active substance with a basic inorganic salt as the active substance, weight percentage of the active substance in the excipient mixture, or the size of the coated microgranule.

On the other hand, JP-A-5-92918 discloses a powder consisting of a fine-particle core coated with a water-soluble high molecular compound and at least one physiologically active substance, and having a granule size of practically up to 500 μm. However, there is no disclosure of an acid-labile physiologically active substance with a basic inorganic salt as the physiologically active substance, weight percentage of the active substance in the coated granule or the size of the coated granule.

JP-A-63-301816 and U.S. Pat. No. 5,026,560 disclose spherical granules having a core coated with spraying powder containing a drug and low substituted hydroxypropylcellulose. However, there is no disclosure of an orally disintegrable tablet.

EP-A-0452862 discloses a spherical granule obtained by coating a pharmacologically inactive spherical seed core having at least 50 weight % microcrystalline cellulose and an average particle size of 100–1000 μm, with a powder comprising an active ingredient, by using an aqueous binding solution, and spraying an aqueous solution or suspension of a coating agent thereon. However, most of the particle sizes of thus obtained granules are 500 μm or more.

JP-A-1-268627, JP-A-1-268628 and JP-A-8-27033 disclose pharmaceutical compositions using erythritol, respectively. However, there is no disclosure of a solid pharmaceutical composition characterized by fast disintegration in the oral cavity.

JP-A-9-48726 discloses a buccal formulation consisting of a drug and a substance wetting in a mouldable way on humidifying, and retaining a shape after moulding and drying. As such substance, sugars, sugar alcohols and water-soluble polymers are exemplified.

JP-A-5-271054 discloses production of fast dissolving tablets comprising an active ingredient and sugars.

JP-A-9-71523 discloses a tablet with rapid disintegration in the oral cavity comprising medicine, crystalline cellulose, low-substituted hydroxypropyl cellulose and lubricant.

However, these prior art references nowhere disclose an acid-labile physiologically active substance with a basic inorganic salt as an active substance, weight percentage of the active substance in the tablet or the size of the coated fine granule.

To accompany an aging population and their changes in life environment, it is desired to develop an orally disintegrable solid preparation capable of being administered without water, retaining the convenience for use which is a characteristic of a tablet, and being administered on demand easily, anytime and anywhere, without water.

Conventional granules have large particle diameters, which results in inferior workability when dispensing, and also results in difficulties in consistently adding a regular amount of the granules when they are combined into tablet or capsules. Granules having a large particle diameter (400 μm or more of average particle diameter) also produce a feeling of roughness in the mouth. Accordingly, especially when used in an orally disintegrable tablet, the average particle a diameter of the included granules must be about 400 μm or less, preferably about 350 μm.

For many reasons, such as, masking a bitter taste, or providing enteric abilities or release abilities, it is desirable to prepare the solid pharmaceutical preparations as granules (or fine granules), In particular, in case of granules or fine granules in which the active ingredient of the drug is enteric coated to impart enteric dissolution, there is a need for enteric coating to prevent dissolution by stomach acid (i.e., to make the preparation acid-resistance). It is necessary to coat the whole surface of the particle—before the enteric coating—(including a case of the crystal of physiologically active substance only, and a case of the granule produced by granulation), with the enteric coating. Namely, at least some uniform thickness (at least 20 μm or more) of the coating layer is needed. Even a portion of thin and weak coating, is undesirable because acid-resistance is lowered. Accordingly, before the enteric coating, it is necessary that the particle is as spherical with as smooth a surface as possible in form, as uniform as possible in size, and has less cavities.

It is very difficult to produce an enteric coated fine granule with an average particle diameter of 400 μm or less, when the coating is performed no that at least 20 μm thickness of coating layer may coat the whole particle, and the enteric coated particle contains a basic inorganic salt for stabilization of an acid-labile physiologically active substance, and where it contains binders for maintaining the strength of the particle and/or disintegrants for maintaining the disintegrability (dissolution) of the particles. Further, in the case where the content of the acid-labile physiologically active substance is increased, it is necessary to also increase the content of the excipients such as basic inorganic salt, binders and disintegrants. Furthermore, it is very difficult to produce a small enteric coated fine granule containing the physiologically active substance in high content.

Accordingly, it is desired to develop a fine granule which is coated with the enteric coating layer on the composition containing the physiologically active substance such as a physiologically active substance containing a basic inorganic salt and which has a particle diameter so that roughness or oral discomfort is not felt, to develop a fine granule containing the physiologically active substance, i.e., the active ingredients of drugs, and so forth, in high content, to develop a fine granule while maintaining enteric dissolution, a disintegrability and dissolution and suitable strength, and to develop an orally disintegrable preparation containing such a fine granule, being a fast disintegration type, showing

superior oral disintegrability and dissolution and having suitable strength (hardness) so that it will not be damaged through production processes or handling.

In particular, there is a need to combine an acid-labile physiologically active substance, with basic inorganic salts and so forth for stability, and further to coat with coating layers such as an enteric layer. In such cases, it is an important problem to produce an small enteric coated fine granule, even though it contains the acid-labile physiologically active substance in high concentration and in high content.

DISCLOSURE OF INVENTION

The present invention relates to:

[1] an orally disintegrable tablet which comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive;

[2] an orally disintegrable tablet of the above [1], wherein the average particle diameter of the fine granules is 300 to 400 μm;

[3] an orally disintegrable tablet of the above [1], wherein the fine granules further comprise a basic inorganic salt;

[4] an orally disintegrable tablet of the above [1], wherein the additive comprises a water-soluble sugar alcohol;

[5] an orally disintegrable tablet of the above [1], wherein the composition coated by an enteric coating layer is further coated by a coating layer which comprises a water-soluble sugar alcohol;

[6] an orally disintegrable tablet of the above [4], wherein the additive comprises (i) crystalline cellulose and/or (ii) low-substituted hydroxypropyl cellulose;

[7] an orally disintegrable tablet of the above [1], wherein the particle diameter of the fine granules is practically 425 μm or less;

[8] an orally disintegrable tablet of the above [1], wherein the particle diameter of the fine granules is practically 400 μm or less;

[9] an orally disintegrable tablet of the above [1], wherein the acid-labile physiologically active substance is a benzimidazole compound or a salt thereof;

[10] an orally disintegrable tablet of the above [9], wherein the benzimidazole compound is lansoprazole;

[11] an orally disintegrable tablet of the above [3], wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium;

[12] an orally disintegrable tablet of the above [1], wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose;

[13] an orally disintegrable tablet of the above [12], wherein the core comprises 50 weight % or more of lactose;

[14] an orally disintegrable tablet of the above [12], wherein the core comprises 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose;

[15] an orally disintegrable tablet of the above [1], wherein the composition comprises 20 weight % or more of an acid-labile physiologically active substance;

[16] an orally disintegrable tablet of the above [1], wherein the composition comprises 20 to 50 weight % of an acid-labile physiologically active substance;

[17] an orally disintegrable tablet of the above [1], wherein the fine granules are produced by fluidized-bed granulation method;

[18] an orally disintegrable tablet of the above [1], wherein the enteric coating layer comprises an aqueous enteric polymer agent;

[19] an orally disintegrable tablet of the above [18], wherein the aqueous enteric polymer agent is a methacrylate copolymer;

[20] an orally disintegrable tablet of the above [18], wherein the enteric coating layer further comprises a sustained-release agent;

[21] an orally disintegrable tablet of the above [20], wherein the sustained-release agent is a methacrylate copolymer;

[22] an orally disintegrable tablet of the above [20], wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent;

[23] an orally disintegrable tablet of the above [4], wherein the water-soluble sugar alcohol is erythritol;

[24] an orally disintegrable tablet of the above [4], wherein the water-soluble sugar alcohol is mannitol;

[25] an orally disintegrable tablet of the above [5], wherein the water-soluble sugar alcohol is in an amount of 5 to 97 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules;

[26] an orally disintegrable tablet of the above [4], wherein the crystalline cellulose is in an amount of 3 to 50 weight % relative to 100 weight % of the tablet apart from the fine granule;

[27] an orally disintegrable tablet of the above [6], wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 7.0 to 9.9 weight %;

[28] an orally disintegrable tablet of the above [6], wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 5.0 to 7.0 weight %;

[29] an orally disintegrable tablet of the above [1], which further comprises crospovidone;

[30] an orally disintegrable tablet of the above [1], wherein the oral disintegration time is one minute or less;

[31] an orally disintegrable tablet of the above [1], which comprises no lubricant inside the tablet;

[32] fine granules having an average particle diameter of 400 μm or less, which comprise a composition coated by an enteric coating layer, said composition having (i) 25 weight % or more of an acid-labile physiologically active substance and (ii) a basic inorganic salt;

[33] fine granules of the above [32], wherein the average particle diameter of the fine granules is 300 to 400 μm;

[34] fine granules of the above [32], wherein the particle diameter of the fine granules is practically 425 μm or less;

[35] fine granules of the above [32], wherein the particle diameter of the fine granules is practically 400 μm or less;

[36] fine granules of the above [32], wherein the acid-labile physiologically active substance is a benzimidazole compound or a salt thereof;

[37] fine granules of the above [36], wherein the benzimidazole compound is lansoprazole;

[38] fine granules of the above [32], wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium;

[39] fine granules of the above [32], wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose;

[40] fine granules of the above [39], wherein the core comprises 50 weight % or more of lactose;

[41] fine granules of the above [32], wherein the composition comprises 25 to 40 weight % of an acid-labile physiologically active substance;

[42] fine granules of the above [32], which are produced by fluidized-bed granulation method;

[43] fine granules of the above [32], wherein the enteric coating layer comprises an aqueous enteric polymer agent;

[44] fine granules of the above [43], wherein the aqueous enteric polymer agent is a methacrylate copolymer;

[45] fine granules of the above [43], wherein the enteric coating layer further comprise a sustained-release agent;

[46] fine granules of the above [45], wherein the sustained-release agent is a methacrylate copolymer;

[47] fine granules of the above [45], wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent;

[48] fine granules of the above [32], wherein the enteric coating layer is in an amount of 50 to 70 weight % relative to 100 weight % of the fine granules;

[49] a tablet, granule, fine granule, capsule, effervescent or suspension preparation which comprises the fine granules of the above [32], and so forth.

In the present specification, "coating" means also partial coating and adhesion or adsorption in addition to coating the whole surface of an object (e.g., core) which is to be coated.

"Spherical" means also forms having a curved surface such as forms having elliptic cross sections, and forms in the shapes of eggplants and drops in addition to spheres.

"Average particle diameter" means volume based distribution median diameter (median diameter: 50% particle diameter from cumulative distribution), unless otherwise specified. It can be measured by, for example, a laser diffraction particle distribution measurement method. Concretely exemplified is a method using Raser Diffraction Analyzer, type: HEROS RODOS [trade name; manufactured by Sympatec (Germany)].

"An orally disintegrable tablet" of the present invention comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive.

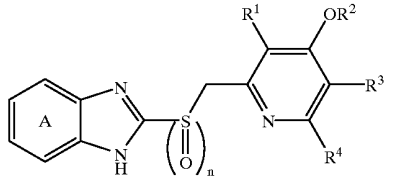
In the present invention, "fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance" have an average particle diameter of about 400 μm or less, in order that roughness is not felt in the mouth. Preferably, the average particle diameter of the fine granules is 300 to 400 μm.

Aside from the average particle diameter of the above "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 425 μm, more preferably 300 to 400 μm.

"Practically" as used in "the particle diameter is practically 425 μm or less" and "the particle diameter is practically 400 μm or less" means that the particles may include a small quantity (about 5 weight % or less) of particles whose particle diameter Is out of above described range to Include the inevitable contaminant particles.

"An acid-labile physiologically active substance" includes a compound being unstable in an acidic region and/or a compound inactivated by an acid, especially a pharmaceutical ingredient. Concretely mentioned are vitamins such as vitamin B_{12}, fursultiamine, folic acid, vitamin A, vitamin D, as well as a known benzimidazole compound having an antiulcer activity of the formula (I) below, or a salt thereof.

Formula (I)



wherein ring A may be substituted; R^1, R^3 and R^4 are the same or different and each is a hydrogen, an alkyl or an alkoxy; R^2 is C_{1-4} alkyl which may be substituted by a substituent(s) selected from the group consisting of halogen, hydroxy and C_{1-4} alkoxy; and n is 0 or 1.

In the above formula (I), "substituent(s)" of the "substituted ring A" include, for example, halogen, C_{1-10} alkyl which may be substituted, C_{3-7} cycloalkyl which may be substituted, C_{2-16} alkenyl which may be substituted, C_{1-10} alkoxy which may be substituted, cyano, carboxy, C_{1-7} alkoxycarbonyl, C_{1-4} alkoxycarbonyl-C_{1-4} alkyl, carbamoyl, carbamoyl-C_{1-14} alkyl, hydroxy, hydroxy-C_{1-7} alkyl, C_{1-6} acyl, carbamoyloxy, nitro, C_{2-6} acyloxy, C_{6-12} aryl, C_{6-12} aryloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, etc.

The "substituent" of the above "C_{1-10} alkyl which may be substituted", "C_{3-7} cycloalkyl which may be substituted", or "C_{2-16} alkenyl which may be substituted" includes, for example, (1) halogen, (2) nitro, (3) amino which may be substituted by 1 or 2 of C_{1-4} alkyl and C_{1-4} acyl, etc., (4) amidino, (5) guanidino, (6) carbamoyl, etc. The number of these substituents is 1 to 3.

The "substituent" of the above "C_{1-10} alkoxy which may be substituted" includes, for example, (1) halogen, (2) nitro, (3) amino which may be substituted by 1 or 2 of C_{1-4} alkyl and C_{1-4} acyl, etc., (4) amidino, (5) guanidino, etc. The number of these substituents is 1 to 3.

The above "C_{1-6} acyl" includes, for example, C_{2-6} alkanoyl such as formyl, acetyl, propionyl, etc.

The above "C_{1-4} acyl" includes, for example, formyl and C_{2-4} alkanoyl such as acetyl, propionyl, etc.

The above "C_{2-6} acyloxy" includes, for example, C_{2-6} alkanoyloxy such as acetyloxyl, etc.

The above "C_{6-12} aryl" includes, for example, phenyl, naphthyl, etc.

The above "C_{6-12} aryloxy" includes, for example, phenoxy, naphthyloxy, etc.

The "alkyl" for R^1, R^3 or R^4 includes, for example, a straight-chain or branched C_{1-10} alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl,

decyl, etc. Among others, preferred is a straight-chain or branched C_{1-6} alkyl. More preferred is a straight-chain or branched C_{1-3} alkyl.

The "alkoxy" for R^1, R^3 or R^4 includes, for example, C_{1-10} alkoxy such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, cyclobutoxy, cyclopentoxy, cyclohexyloxy, etc. Among others, preferred is C_{1-6}alkoxy. More preferred is C_{1-3} alkoxy.

The "C_{1-4} alkyl" of the "C_{1-4} alkyl which may be substituted by a substituent(s) selected from the group consisting of halogen, hydroxy and C_{1-4} alkoxy" for R^2 includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, etc.

The "C_{1-4} alkoxy" of the above "C_{1-4} alkyl which may be substituted by a C_{1-4} alkoxy" includes, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.

The number of the substituents which the "C_{1-4} alkyl" has is preferably 1 to 3.

Salts of the benzimidazole compound include pharmaceutically acceptable salts such as alkali metal salts, e. g., sodium salts and potassium salts, alkaline earth metal salts e. g., calcium salts and magnesium salts, etc.

Such benzimidazole compounds having an antiulcer activity, or salts thereof include, for example, a compound or a salt thereof disclosed in JP-A-52-62275, JP-A-54-141783 JP-A-57-53406, JP-A-58-135881, JP-A-58-192880, JP-A-59-181277, JP-A-61-50978, JP-A-62-116576, JP-A-62-277322, JP-A-62-258320, JP-A-62-258316, JP-A-64-6270, JP-A-64-79177, JP-A-5-59043, JP-A-62-111980, JP-A-5-117268, EP-A-166287, EP-A-519365, and so forth.

The "physiologically active substance" of the present invention preferably is a benzimidazole compound or a salt thereof such an tenooprdzole, omneirazole, rabmprazole, pantoprazole, perprazole, leminoprazole, TU-199, etc. Preferred is lansoprazole and omeprazole, etc. More preferred is lansoprazole.

The amount of the "acid-labile physiologically active substance" in the "composition" is, for example, about 10 weight % or more, preferably about 20 weight % or more, more preferably about 23 weight % or more, especially preferably about 25 weight % or more. Among others, preferred is 20 to 50 weight %.

In the "composition", a basic inorganic salt is preferably incorporated with the acid-labile physiologically active substance.

The "basic inorganic salt" includes, for example, a basic inorganic salt of sodium, potassium, magnesium and/or calcium, preferably a basic inorganic salt of magnesium and/or calcium. Among others, preferred is a basic inorganic salt of magnesium.

The basic inorganic salt of sodium includes, for example, sodium carbonate, sodium hydrogencarbonate, etc.

The basic inorganic salt of potassium includes, for example, potassium carbonate, potassium hydrogencarbonate, etc.

The basic inorganic salt of magnesium includes, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metagilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16}.CO_3.4H_2O$], aluminum magnesium hydroxide [$2.5MgO.Al_2O_3.xH_2O$], etc. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc.

The basic inorganic salt of calcium includes, for example, precipitated calcium carbonate, calcium hydroxide, etc.

The preferable examples of the "basic inorganic salt" include heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc.

Such basic inorganic salt of magnesium or calcium, etc. has a basic pH (not less than 7) when it is in the form of a 1% aqueous solution or suspension.

Two or more of these basic inorganic salts (preferably a basic inorganic salt of magnesium, a basic inorganic salt of calcium, etc.) can be used as a mixture in a given ratio. The amount of the basic inorganic salt to be used is appropriately selected depending on the kind of the basic inorganic salt and is, for instance, about 0.3 to 200 weight %, preferably about 1 to 100 weight %, more preferably about 10 to 50 weight %, especially preferably about 20 to 40 weight % relative to the benzimidazole compound or a salt thereof.

The "composition" may contain water-soluble polymers, the following binders, lubricants, and excipients, etc. in common use as pharmaceutical materials. The amount of such water-soluble polymers, binders, lubricants, and excipients is selected from amounts commonly employed in the manufacture of preparations in general dosage forms.

The "water-soluble polymer" includes, for example, a water-soluble polymer which is soluble in ethanol (i.e., an ethanol-soluble water-soluble polymer) such as a cellulose derivative (e.g., hydroxypropyl cellulose, which may be referred to as "HPC" hereinafter), poly(vinylpyrrolidone), etc.; a water-soluble polymer which is insoluble in ethanol (i.e., an ethanol-insoluble water-soluble polymer) such as a cellulose derivative (e.g., hydroxypropylmethyl cellulose, which may be referred to as "HPMC" hereinafter, methyl cellulose, carboxymethyl cellulose sodium, etc.), sodium polyacrylate, polyvinyl alcohol, sodium alginate, and guar gum, etc.

When such water-soluble polymers are used, the dissolution of drugs (physiologically active substances) can be controlled by employing them in combination with the ethanol-soluble water-soluble polymer and ethanol-insoluble water-soluble polymer or by employing them in combination with some water-soluble polymers having different viscosity.

In the present invention, the "water-soluble polymer" is preferably, a cellulose derivative such as HPC, HPMC, and methyl cellulose, and polyvinyl alcohol. More preferred is a cellulose derivative such as HPC, HPMC.

The "HPC" contains, for example, about 53.4 to 77.5 weight %, more preferably about 60 to 70 weight %, of hydroxypropoxyl group. The viscosity of 2 weight % aqueous solution of HPC at 20° C. is usually about 1 to 150,000 cps (centipoise). As the above HPC, hydroxypropyl cellulose defined in Japanese Pharmacopoeia may be employed. Hereinafter, all viscosity of HPC is a value of 2 weight % aqueous solution at 20° C.

The "HPMC" is a mixed ether which is connected by a methoxy group and a hydroxypropoxy group. The content of the methoxy group of HPMC is, for example, about 19 to 30 weight %, The content of the hydroxypropoxy group is, for example, about 4 to 12 weight %. The viscosity of 2 weight % aqueous solution of HPMC at 20° C. is usually about 1 to 40,000 centistokes. As such HPMC may be employed hydroxypropylmethyl cellulose 2208 defined by Japanese Pharmacopoeia, hydroxypropylmethyl cellulose 2906 defined by Japanese Pharmacopoeia, hydroxypropylmethyl cellulose 2910 defined by Japanese Pharmacopoeia, and so forth. Hycroxypropyl cellulose(s) may be employed alone or in admixture of two or more thereof.

The content of the water-soluble polymer such as HPC and/or HPMC is usually about 0.1 to 50 weight %, preferably about 1 to 30 weight %, as against the whole "composition" containing the physiologically active substance, in order to control the dissolution of the physiologically active substance in the composition containing the physiologically active substance and retain a high content of the physiologically active substance.

The above "enteric coating layer" which coats the "composition having 10 weight % or more of an acid-labile physiologically active substance" includes, for example, an aqueous enteric polymer agent such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (hereinafter, referred to as HP-55), hydroxymethyl cellulose acetate succinate, methacrylate copolymer [e.g., Eudragit L30D-55 etc. (trade name; manufactured by Rohm GmbH (Germany)), KollICoat MAE30DP (trade name; manufactured by BASF (Germany)), Polyquid PA-30 (trade name; manufactured by SanyoKasei (Japan)), etc.], carboxymethyl cellulose, shellac, etc.; a sustained-release agent such as methacrylate copolymer [e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name), etc.]; a water-soluble polymer; plasticizers such as triethyl citrate, polyethylene glycol, acetylatedmonoglyceride, triacetin, castor oil, etc. and mixtures thereof.

The "aqueous enteric polymer agent" is preferably a methacrylate copolymer. The "sustained-release agent" is preferably a methacrylate copolymer.

The "sustained-release agent" is used in an amount of 5 to 30 weight %, preferably 5 to 15 weight %, relative to 100 weight % of the "aqueous enteric polymer agent". The "plasticizers" is used in an amount of 5 to 30 weight% relative to 100 weight % of the "aqueous enteric polymer agent".

The "additives" of the "orally disintegrable tablet which. comprises (i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer, said composition having 10 weight % or more of an acid-labile physiologically active substance and (ii) an additive" may be ones commonly employed as pharmaceutical materials. The amount of such additives to be used is selected from amounts commonly employed in the manufacture of preparations in general dosage forms.

The "additives" include, for example, a water-soluble sugar alcohol, a crystalline cellulose, a low-substituted hydroxypropyl cellulose, as well as, binders, acids, foaming agents, artificial sweeteners, flavorants, lubricants, colorants, stabilizers, excipients, disintegrants, and so forth.

The "water-soluble sugar alcohol" means a water-soluble sugar alcohol which needs water in an amount of less than 30 ml when 1 g of water-soluble sugar alcohol is added to water and dissolved within about 30 minutes at 20° C. by strongly shaking every 5 minutes for 30 seconds.

The "water-soluble sugar alcohol" includes, for example, sorbitol, mannitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose, erythritol, etc. Two or more of these water-soluble sugar alcohols can be used as a mixture in a given ratio.

The "water-soluble sugar alcohol" is preferably mannitol, xylitol and erythritol. More preferred is mannitol and erythritol. Especially preferred is mannitol. As erythritol, one that is produced by fermentation with yeasts using glucose as the starting material, and that has a particle size of at most 50 mesh is used. Such erythritol is available on the market, e.g. as manufactured by Nikken Chemical Co., Ltd. (Japan).

The "water-soluble sugar alcohol" is usually employed in an amount of about 5 to 97 weight %, preferably about 10 to 90 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules, in order to obtain sufficient strength of the preparation and sufficient disintegration or dissolution in the oral cavity.

For example, mannitol or erythritol is usually employed in an amount of about 5 to 90 weight %, preferably about 10 to 80 weight %, more preferably about 20 to 80 weight %, especially preferably about 50 to 80 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

The "crystalline cellulose" includes refined one having partially α-cellulose depolymerization. Such crystalline cellulose includes one called microcrystalline cellulose. Examples of the "crystalline cellulose" include CEOLUS KG801, avicel PH101, avicel PH102, avicel PH301, avicel PH302, avicel RC-591 (crystalline cellulose carmellose sodium), etc. Among these, preferably employed is CEOLUS KG801 which is also called crystalline cellulose of high compressibility. Two or more of the crystalline cellulose can be used as a mixture in a given ratio. Such crystalline cellulose is available on the market, for example, as manufactured by Asahi Chemical Co., Ltd. (Japan).

The "crystalline cellulose" is used, for instance, in an amount of about 3 to 50 weight %, preferably about 5 to 40 weight %, more preferably about 5 to 20 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

The "low-substituted hydroxypropyl cellulose" means a low-substituted hydroxypropyl cellulose wherein the content of hydroxypropoxyl group in the hydroxypropyl cellulose (hereinafter,maybe abbreviated to "the content of HPC group") is about 5.0 to 9.9 weight %, preferably a low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0 weight %, a low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9 weight %, and so forth.

The "low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9% includes, for example, LH-22, LH-32 and mixtures thereof, which are commercially available [Shin-Etsu Chemical Co., Ltd. (Japan)]. Also, they can be produced in accordance with per se known methods, for example, methods described in JP-B-82 53100 or analogous thereto.

The low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0% includes, for example, LH-23, LH-33 and mixtures thereof, described in the following Reference Examples. They can be produced in accordance with per se known methods, for example, methods described in JP-B-82 53100 or analogous thereto.

At first, alkaline cellulose containing free alkaline and propylene oxide is reacted to obtain the crude low-substituted hydroxypropyl cellulose containing free alkaline.

Concretely, for example, raw material pulp such as wood pulp and cotton leader is immersed in about 10 to 50% concentration of an aqueous solution of sodium hydroxide, and pressed to obtain alkaline cellulose of which NaOH/cellulose ratio is about 0.1 to 1.2 (ratio by weight). Next, crude low-substituted hydroxypropyl cellulose containing free alkaline is obtained by reacting the resulting alkaline cellulose and propylene oxide with stirring at about 20 to 90° C. for about 2 to 8 hours. Propylene oxide is used in an amount so that the content of hydroxypropoxyl group in the desired low-substituted hydroxypropyl cellulose can be 5 or more weight % to less than 7 weight % (in case of the

low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 5.0 to 7.0 weight %), 7 or more weight % to less than 9.9 weight % (in case of the low-substituted hydroxypropyl cellulose wherein the content of HPC group is about 7.0 to 9.9 weight %).

The crude low-substituted hydroxypropyl cellulose containing free alkaline is dispersed in water or hot water containing about 5 to 80% of acid necessary to neutralize all the alkaline, and a part of the crude low-substituted hydroxypropyl cellulose containing free alkaline is dissolved therein. Acid is further added to neutralize the remaining alkaline.

After the neutralization, some processes such as drainage, drying and grinding are performed in accordance with conventional methods to obtain the desired low-substituted hydroxypropyl cellulose.

The particle diameter of "the low-substituted hydroxypropyl celluloses wherein the content of hydroxypropoxyl group is 5.0 to 7.0 weight %" to be used in the present invention is, for example, about 5 to 60 Sm. preferably about 10 to 40 μm, as a average particle diameter.

In the above ranges, in case that low-substituted hydroxypropyl celluloses (L-HPC) having a relatively large particle diameter (for example, L-HPC having about 26 to 40 μm of the average particle diameter) is employed, a pharmaceutical preparation superior in disintegrability can be produced. On the other hand, in case that L-HPC having a relatively small particle diameter (for example, L-HPC having about 10 to 25 μm of the average particle diameter) is employed, a pharmaceutical preparation superior in strength of the preparation can be produced. Accordingly, the particle diameter of L-HPC can be suitably selected according to the characteristics of the desired pharmaceutical preparation.

The "low-substituted hydroxypropyl cellulose wherein the content of HPC group is 5.0 to 7.0 weight %" or the "low-substituted hydroxypropyl cellulose wherein the content of HPC group is 7. 0 to 9.9%" is usually employed in an amount of about 3 to 50 weight %, preferably about 5 to 40 weight %, relative to 100 weight % of the orally disintegrable tablet apart from the fine granules, in order to obtain sufficient oral disintegrability and sufficient strength of the preparation.

The "binders" include, for example, hydroxypropyl cellulose, hyaroxypropylmethylcellulose, crystalline cellulose, α starch (pregelatinized starch), polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, low-substituted hydroxypropyl cellulose, etc. The use of crystalline cellulose as the binders provides a solid preparation which exhibits more excellent strength of a preparation while retaining excellent disintegration and dissolution in the oral cavity.

The "acids" include, for example, citric acid (e.g., citric acid anhydrous), tartaric acid, malic acid, etc.

The "foaming agents" include, for example, sodium hydrogen carbonate, etc.

The "artificial sweeteners" include, for example, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, thaumatin, etc.

The "flavorants" include synthetic flavorants or natural flavorants, such as lemon, lime, orange, menthol, strawberry, etc.

The "lubricants" include, for example, magnesium stearate, sucrose fatty acid ester, polyethyleneglycol, talc, stearic acid, etc.

The "colorants" include, for example, various food colorants such as Food Yellow No. 5, Food RED No. 2, Food Blue No. 2, etc., food lakes, red iron oxide, etc.

The "stabilizers" include, for example, the above-mentioned "basic inorganic salt".

The "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride, titanium oxide, etc.

The "disintegrants" include those conventionally used in the pharmaceutical field, such as (1) crospovidone, (2) super disintegrants such as croscarmellose sodium [FMC-Asahi Chemical Co., Ltd. (Japan)], carmellose calcium [Gotoku Chemical(Yakuhin), (Japan)], (3) carboxymethylstarch sodium [e.g., Matsutani Chemical Co., Ltd. (Japan)], (4) low-substituted hydroxyDropyl cellulose e.g., Shin-Etgu Chemical Co., Ltd. (Japan)], (5) corn starch, etc. Among others, preferred is, for example, crospovidone.

The "crospovidone" includes polyvinylpolypyrrolidone (PVPP), 1-vinyl-2-pyrrolidinone homopolymer, 1-ethenyl-2-pyrrolidinone homopolymer, etc, such as Kollidon CL [manufactured by BASF (Germany)], Polyplasdone XL [manufactured by ISP Ltd. (Japan)], Polyplasdone XL-10 [manufactured by ISP Ltd. (Japan)], Polyplasdone INF-10 [manufactured by ISP Ltd. (Japan)], etc. Usually crospovidone having a molecular weight of at least 1,000,000 is used.

Two or more of these disintegrants can be as a mixture in a given ratio. For example, (i) crospovidone solely, or (ii) crospovidone and another disintegrant(s) is preferably employed.

The "disintegrants" are used, for instance, in an amount of about 1 to 15 weight %, preferably about 1 to 10 weight %, more preferably about 3 to 7 weight %, relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

In the present invention, the "fine granules" may contain, for example, titanium oxide as a masking agent.

The diameter of the "orally disintegrable tablet" of the present invention is about 5 to 20 mm, preferably about 7 to 15 mm, more preferably about 8 to 13 mm.

The "orally disintegrable tablet" may comprise no lubricant inside the tablet.

The "orally disintegrable tablet" of the present invention exhibits fast disintegrability or dissolubility in the oral cavity, and also an appropriate strength of preparation.

The oral disintegration time of the "orally disintegrable tablet" of the present invention (the time for healthy male or female adults to complete disintegration by buccal saliva) is one minute or less, usually about 50 seconds or less, preferably about 40 seconds or less, more preferably about 30 seconds or less.

The strength of the "orally disintegrable tablet" of the present invention (measurement with a tablet hardness tester) is usually about 1 to 20 kg, preferably about 2 to 15 kg, more preferably 3 to 8 kg.

In the above-mentioned fine granules, "fine granules having an average particle diameter of 400 pzn or less, which comprise a composition coated by an enteric coating layer, said composition having (i) 25 weight % or more of an acid-labile physiologically active substance and (ii) a basic inorganic salt" are novel.

The "fine granules" have an average particle diameter of about 400 μm or less, preferably 350 μm or less. Preferably; the average particle diameter of the fine granules is 300 to 400 μm. Aside from the average particle diameter of the "fine granules", regarding the maximum particle size, the particle diameter is practically 425 μm or less, and preferably practically 400 μm or less. Preferably, the particle diameter is practically 300 to 400 μm or less.

Regarding the fine granule of the present invention, the dissolution of the physiologically active substance can be

controlled by formulating the coat (coating layer) to have different viscosity or content of the water-soluble polymer (e.g., HPC, HPMC and so forth) or by formulating the coat to have a controlled ratio of the ethanol-soluble water-soluble polymer (e.g., HPC) and the ethanol-insoluble water-soluble polymer (e.g., HPMC). The dissolution of the physiologically active substance is not very influenced by liquidity, which can be suitably controlled.

As a pharmaceutical preparation which comprises the "fine granules" of the present invention, there may be employed, for example a solid preparation such as tablet, granule, fine granule, capsule, effervescent, etc; a liquid preparation such as suspension preparation, etc. Among others, preferred is a tablet, more preferred is an orally disintegrable tablet.

When the "fine granule" of the present invention is used for a tablet except for an orally disintegrable tablet, the diameter of the tablet is about 5 to 10 mm, preferably about 5 to 8 mm. When the fine granule of the present invention is used for a capsule, the size of the capsule is preferably a #2 capsule or less.

The "orally disintegrable tablet" of the present invention is and the "pharmaceutical preparation which comprises the fine granules of the present invention" may contain a foaming component to impart a refreshing feeling at administration. Also, with an effervescent comprising the foaming component, the dissolution can be precisely controlled compared to the case of a fine granule alone. As the foaming component, various compounds can be employed as long as safety is not interfered with. Examples of the foaming component include alkaline metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), alkaline metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.) and ammonium carbonate and so forth. The foaming component(s) may be employed alone or in an admixture of two or more thereof. The preferable foaming component includes sodium carbonate, sodium hydrogencarbonate, ammonium carbonate and so forth. The ratio of the foaming component can be selected within the range in which it is possible to impart the foam, for example, about 10 to 2500 weight %, preferably about 50 to 2000 weight % (e.g., about 75 to 1500 weight %), more preferably about 100 to 1000 weight %, relative to 100 weight % of the fine granule.

In employing the effervescent and the fine granule having small particle diameter, it is advantageous to quickly prepare a homogeneous aqueous solution or suspension, and to maintain the dispersed condition. But, in case that the particle diameter is too small, the problem tends to occur that the fine granule adheres to the wall of a machine by static electricity during production processes.

The specific volume of the above fine granule is about 3 ml/g or less, preferably about 2 ml/g or less. In order to maintain the homogeneous condition of the fine granule in the suspension obtained by adding the foaming agent composition, the specific volume can be suitably selected in the above range according to the specific gravity (specific volume) of the dispersion medium.

The "composition" in the present invention can be produced by a known granulation method.

The "granulation method" includes, for example, rolling granulation method (e.g., centrifugal rolling granulation, etc.), fluidized-bed granulation (e.g., rolling fluidized bed granulation, fluidized granulation, etc.), stirring granulation and so forth. Among others, preferred is fluidized-bed granulation method, more preferred is rolling fluidized-bed granulation method.

Concrete example of the "rolling granulation method" includes a method using "CF apparatus" manufactured by Freund Industrial Co., Ltd. (Japan) and so forth. Concrete examples of the "rolling fluidized-bed granulation method" include methods using "SPIR-A-FLOW", "multi plex" manufactured by Powrex Corp. (U.S.A.), "New-Marumerizer" manufactured by Fuji Paudal Co., Ltd. (Japan), and so forth. The method for spraying the mixture can be suitably selected in accordance with the kind of granulator, and may be, for example, any one of a top spray method, a bottom spray method, a tangential spray method, and so forth. Among others, a tangential spray method is preferred.

The "composition" in the present invention. can be produced in accordance with, for example, a method which comprises coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance.

For example, employed is a method described in JP-A-5-92918 (coating method), which comprises coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance, if necessary together with a basic inorganic salt, binders, lubricants, excipients, a water-soluble polymer, etc. (hereinafter, may be abbreviated to "coating layer"). For example, employed is a method which comprises coating a core with an acid-labile physiologically active substance and a basic inorganic salt, and then further with binders, lubricants, excipients, a water-soluble polymer, etc.

The average particle diameter of the "cores" is about 250 μm or less, preferably about 50 to 250 μm, more preferably about 100 to 250 μm, especially preferably about 100 to 200 μm. The "cores" having the above average particle diameter include particles which all pass through a #50 sieve (300 μm), particles where about 5 w/w % or less of the total remain on a #60 sieve (250 μm), and particles where about 10 w/w % or less of the total pass through a #282 sieve (53 μm) The specific volume of the "core" is about 5 ml/g or less, preferably about 3 ml/g or less.

Examples of the "core" include

(1) a spherical granulated product comprising crystalline cellulose and lactose, (2) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (avicel SP, manufactured by Asahi Chemical Co., Ltd. (Japan)), (3) a stirring granulated product being about 50 to 250 μm and comprising lactose (9 parts) and a starch (1 part), (4) a micro particle being about 250 μm or less classified as a spherical granule comprising micro crystalline cellulose described in JP-A-61-213201, (5) a processed product such as wax formed to a sphere by spraying or melting granulation, (6) a processed product such as gelatin beads comprising oil component, (7) calcium silicate, (8) starch, (9) a porous particle such as chitin, cellulose, chitosan, etc, and (10) a bulk product such as granulated sugar, crystalline lactose or sodium chloride, and processed preparations thereof. Further, these cores may be produced in accordance with per se known grinding method or granulation method, and sifted to prepare the particles having the desired particle diameter.

The above "spherical granulated product comprising crystalline cellulose and lactose" includes, for example (i) a spherical granulated product being 100 to 200 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) [e.g., Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm), manufactured by Freund Industrial Co., Ltd. (Japan)], (ii) a spherical granulated product being about 150

to 250 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) [e.g., Nonpareil NP-7:3, manufactured by Freund Industrial Co., Ltd. (Japan)], (iii) a spherical granulated product being 100 to 200 μm and comprising crystalline cellulose (4.5 parts) and lactose (5.5 parts) [e.g., Nonpareil 105T (70–140) (particle diameter of 100 to 200 μm), manufactured by Freund Industrial Co., Ltd. (Japan)], (iv) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (5 parts) and lactose (5 parts) [e.g., Nonpareil NP-5:5, manufactured by Freund Industrial Co., Ltd. (Japan)], and so forth.

In order to produce a pharmaceutical preparation which is superior in dissolution while retaining suitable strength, the "core" includes, for example, preferably the spherical granulated product comprising crystalline cellulose and lactose, more preferably the spherical granulated material comprising crystalline cellulose and lactose and containing 50 weight % or more of lactose. Among others, preferred in a core comprising 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose.

As the "core" employed in the present invention, in particular, there may be employed the spherical granulated product comprising crystalline cellulose and lactose, more preferably the spherical granulated product with a diameter of about 100 to 200 μm and comprising crystalline cellulose (4.5 parts) and lactose (5.5 parts).

The "core" may contain the physiologically active substance such as the above described pharmaceutical ingredient. Also, the "core" may not contain the physiologically active substance because the release of the physiologically active substance can be controlled by a coating layer containing the physiologically active substance.

The "core" is preferably as uniform a sphere as possible, for reducing the irregularity of the coating, in addition to being a powdery core.

The ratio of the "coating layer" to the "core" can be selected within the range in which it is possible to control dissolution of the physiologically active substance and particle size of the composition, for example, usually about 50 to 400 weight % relative to 100 weight % of the core.

The coating layer may be constructed by plural layers. At least one layer of the plural layers must contain the physiologically active substance. The combination of various layers such as a coating layer not containing the active ingredient, a base coating layer, and an enteric coating layer which constitute the coating layer can be suitably selected.

In case that the "core" is coated, for example, the above physiologically active substance and the water-soluble polymer can be employed in admixture thereof. The admixture may be a solution or a dispersion, and can be prepared by using an organic solvent such as water or ethanol or an admixture thereof.

The concentration of the water-soluble polymer in the admixture varies according to the ratio of the physiologically active substance and the excipients, and is usually about 0.1 to 50 weight %, preferably about 0.5 to 10 weight %, in order to retain the binding strength of the physiologically active substance to the core and maintain the viscosity of the mixture so as not to reduce the workability.

Where the coating layer comprises plural layers, the concentration of the physiologically active substance in each layer may be changed successively or gradually by selecting for the content ratio or viscosity of the water-soluble polymer or by successive coating with mixtures varying in the ratio of the physiologically active substance and the other excipients. In the above case, it may be coated with a mixture in which the content ratio of the water-soluble polymer is out of the range of about 0.1 to 50 weight %, as long as the coating layer as a whole contains about 0.1 to 50 weight % of the water-soluble polymer. Further, in forming the inactive coat according to known methods, the coating layer may comprise some layers such that the inactive layer may block each layer containing the physiologically active substance.

Also, in case of two or more physiologically active substances not suited in the compatibility, the core may be coated by employing each mixture together or separately.

The above coated material is dried, and passed through sieves to obtain a "composition" having uniform size. Because the form of the powder is usually according to the core, a fine granule being in the form of a rough sphere may be obtained. As the sieve may be employed, for example a #50 circular sieve (3001 μm). The composition is obtained by selecting those which pass through the #50 circular sieve.

The "fine granule" in the present invention can be produced in accordance with in the same manner as above granulation method, for example, a method which comprises coating the composition with an enteric coating layer, in order to protect the acid-labile physiologically active substance or to impart enteric dissolution. If necessary, the composition coated with an enteric coating layer may be further coated by a water-soluble sugar alcohol, preferably mannitol. In such case, the strength of the orally disintegrable tablet comprising fine granules is improved.

The "enteric coating layer" is preferably a layer having about 20 to 70 μm, preferably about 30 to 50 μm of thickness and coating the whole surface of the composition containing the physiologically active substance. Accordingly, the smaller particle diameter of the composition, the higher the weight % of the enteric coating layer in the whole fine granule. In the fine granule of the present invention, the "enteric coating layer" is about 30 to 70 weight %, preferably about 50 to 70 weight %, of the fine granule as a whole.

The "enteric coating layer" may be constructed by plural (e.g., 2 or 3) layers. For example, employed is a method which comprises coating a composition with an enteric coating layer having polyethyleneglycol, and then with an enteric coating layer having triethyl citrate, followed by being coated with an enteric coating layer having polyethyleneglycol.

The "orally disintegrable tablet" of the present invention can be produced in accordance with a conventional method in the pharmaceutical field. Such methods include, for instance, a method which comprises blending the "fine granules" and the "additives", and molding, if necessary followed by drying. Concretely mentioned is a method which comprises blending the fine granules and the additives, if necessary with water, and molding, if necessary followed by drying.

The "blending procedure" can be carried out by any of the conventional blending techniques such as admixing, kneading, granulating, etc. The above "blending procedure" is carried out, for instance, by using an apparatus such as Vertical Granulator GV10 [manufactured by Powrex Corp. (Japan)], Universal Kneader [manufactured by Hata Iron Works Co., Ltd. (Japan)], fluidized bed granulator LAB-1 and FD-3S [manufactured by Powrex Corp. (Japan)], V-shape mixer, tumbling mixer, and so forth.

Preferred example of the method for the "orally disintegrable tablet" of the present invention is a method which comprises:

(i) coating a core comprising crystalline cellulose and lactose with an acid-labile physiologically active substance and a basic inorganic salt, followed by being

coated with a coating layer comprising a water-soluble polymer to obtain a composition,

(ii) coating the resultant composition with an enteric coating layer having polyethyleneglycol, and then with an enteric coating layer having triethyl citrate, and then with an enteric coating layer having polyethyleneglycol, followed by being coated by mannitol to obtain fine granule, and

(iii) blending the resultant fine granule with an additive, followed by molding.

Where the pharmaceutical preparation of the present invention, especially an orally disintegrable tablet, is one which comprises no lubricant inside the preparation or tablet, such preparation can be preferably produced in accordance with methods described in JP-A-56-14098, Japanese Patent No. 2681601, etc. Such preparation, especially an orally disintegrable tablet, has sufficient strength. The above lubricant includes, for example, magnesium stearate, sucrose fattyacid ester, polyethyleneglycol, talc, stearic acid, etc.

The pharmaceutical preparations such as solid preparation (e.g., tablets, granules, fine granules, capsules, effervescents, etc.) and liquid preparation such as suspending preparation, which comprises the "fine granules" of the present invention can be produced in accordance with a conventional method.

The solid pharmaceutical preparation containing the "fine granules" of the present invention and the "orally disintegrable tablet" of the invention can also be produced by the wet tabletting method. As the above method, it is preferably employed the methods described in JP-A-5-271054 and so forth. They can also be produced by drying after humidification. As the above method, preferably employed are the methods described in JP-A-9-48726, JP-A-8-291051 and so forth. Namely, it is effective to humidify before tabletting or after tabletting and then to dry, in order to enhance the hardness.

The "molding procedure" can be carried out, for instance, by tabletting with a pressure of 0.5 to 3 ton/cm^2, preferably 1 to 2 ton/cm^2 by using a single-punch tabletting machine [Kikusui Seisakusho (Japan)] or a rotary type tabletting machine [Kikusui Seisakusho (Japan)] when a solid preparation is a tablet, especially an orally disintegrable tablet.

The "drying procedure" can be carried out by any of the techniques used commonly in the art, such as vacuum drying, fluidized-bed drying, etc.

The "fine granules" of the invention can be used for a pharmaceutical preparation. The pharmaceutical preparation includes, for example, a solid preparation such as tablet, granule, fine granule, capsule, effervescent, etc.; a liquid preparation such as a suspension preparation, etc. Among others, a tablet is preferred. Such tablet preferably has suitable strength so as to be stable through production processes and distributions.

A solid pharmaceutical preparation comprising the fine granule of the invention is used for an orally disintegrable tablet and can be administered without water or together with water.

As administration methods, there are listed (1) a method of administration by dissolution or disintegration together with a little water, or without water and with saliva in the oral cavity, not to be swallowed as it is, or (2) a method of administration with water, where it is swallowed as it is. Also, the tablet may be administered dissolved or disintegrated with water.

The "orally disintegrable tablet" of the present invention is advantageously used in (a) cases where administration without water is necessary, (b) cases of administration to a patients who have difficulty in swallowing tablets, or (c) cases of administration to the aged or to children where there is a fear of blocking the throat if it is in usual tablet form.

In case of the above (a), the orally disintegrable tablet is preferably used for antipyretic agents, analgesic agents, anti-inflammatory agents, antianxiety drugs, antitussive-expectorants, anti motion sickness agents, drugs for prevention and treatment for car-sickness, and so forth.

In case of the above (b), the orally disintegrable tablet is preferably used for preventing and/or treating hypertension, hyperlipemia, diabetes, bronchial asthma, cerebrovascular diseases, and so forth.

The "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention can be safely administered orally to mammals such as mice, rats, rabbits, cats, dogs, bovines, horses, monkeys, humans, etc.

With the dosage of the "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention, varies depending on the pharmaceutically active ingredient, subject, kinds of diseases, etc., the dosage can be selected so that the dosage of the pharmaceutically active ingredient is an effective amount.

For instance, when a benzimidazole compound (I) or a salt thereof such as lansoprazole is employed as an acid-labile physiologically active substance, especially a pharmaceutically active ingredient, the "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention is useful for treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, anastomotic ulcer, Zollinger-Ellison syndrome, etc), gastritis, reflux esophagitis, etc.; eradication of *H. pylori;* suppression of gastrointestinal bleeding caused by digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of gastrointestinal bleeding caused by invasive stress (e.g., stress caused by cerebrovascular disease, head injury, failure of many organs, burn injury of a wide range, which necessitate a large-scale operation necessitating the following intensive management, or intensive care); treatment and prevention of ulcer caused by non-steroidal anti-inflammatory agent; treatment and prevention of gastric hyperacidity and ulcer caused by postoperative stress; administration before anesthesia, etc. The dosage of the preparation per an adult (body weight: 60 kg) is about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, as a benzimidazole compound (I) or a salt thereof such as lansoprazole.

The "orally disintegrable tablet" of the present invention and the pharmaceutical preparation which comprises the "fine granules" of the present invention can be administered once a day, or two or three times separately a day.

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples and Reference Examples are further illustrative but by no means limitative of the present invention.

Unless otherwise specifically indicated, the following "%" means weight %.

Also, the content of the hydroxypropoxyl group is measured in accordance with the methods described in Japanese Pharmacopoeia (13th edition).

The physical properties of the tablets and granules prepared in Examples were determined by the following test methods.

(1) Hardness Test

Determination was carried out with a tablet hardness tester [manufactured by Toyama Sangyo, Co. Ltd. (Japan)]. The test was performed in 10 runs and mean values were shown.

(2) Oral Disintegration Time

Time for complete disintegration only by saliva in the oral cavity was determined.

(3) Remaining Ratio

According to the 2nd method of the dissolution test defined in Japanese Pharmacopoeia, the dissolution test was performed by using 500 ml of 0.1N HCl (75 rpm) for 1 hour. Then, the enteric fine granule was collected by means of the sieve. The content of the drug in the collected fine granule was measured by the HPLC method. The remaining ratio was calculated according to the following expression with the content of the drug in the tablet which is measured separately by HPLC method.

Remaining ratio=(Content of the drug in the collected fine granule after the dissolution test using 0.1N HCl for 1 hour)/(Content of the drug in the tablet)

(4) Acid-resistance: Dissolution using 0.1N HCl

According to the 2nd method of the dissolution test defined in Japanese Pharmacopoeia, the dissolution test was performed by using 500 ml f 0.1N HCl (75 rpm) for hour. Then, test medium was collected and filtered by using a 0.45 μm membrane filter. The absorbance way measured to calculate the dissolution of the drug into 0.1N HCl.

(5) Average Particle Diameter: Volume Based Distribution Median Diameter (median diameter: 50% Particle Diameter from Cumulative Distribution)

Determination was carried out with Raser Diffraction Analyzer, type; HEROS RODOS [trade name, manufactured by Sympatec (Germany)].

EXAMPLES

Example 1

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 300 g of Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 28° C. respectively, the Nonpareil is coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation is stopped when the specified amount of the bulk liquid has been sprayed, and then drying is carried out in the granulator for 7 minutes. The resulting granules are sieved through a #60 circular sieve (250 Am) and a #100 circular sieve (150 μm) to provide 750 g of granules having a core.

Bulk Liquid:

Lansoprazole	300 g
Magnesium carbonate	100 g
L-HPC	50 g
HPC (Type SSL)	100 g
Water	1650 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 680 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70°0 C. and about 36° C., respectively, an undercoating liquid of the following composition prepared in advance is sprayed in accordance with the tangential spray method at a spray rate of 10 g/min. to provide 650 g of film-undercoated granules having a core.

Undercoating Liquid:

HPMC (Type 2910, viscosity: 3 centistokes)	32 g
Talc	8 g
Water	760 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] is charged with 450 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 36° C., respectively, an enteric film coating liquid of the following composition prepared in advance is sprayed in accordance with the tangential spray method at a spray rate of 17 g/min. The coated powders are dried in vacuum at 40° C. for 16 hours, and sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 950 g of enteric coated granules having a core.

Enteric Film Coating Liquid:

Eudragit L30D-55	1078.3 g
Eudragit NE30D	138.5 g
Triethyl citrate	46.0 g
Glyceryl monostearate	23.1 g
Talc	16.0 g
Polysorbate 80	9.0 g
Yellow iron oxide	0.5 g
Water	2038.5 g

Sieve	weight ratio
#18 (850 μm) on	0%
#30 (500 μm) on	0%
#200 (75 μm) on	100%
#200 (75 μm) pass	0%

(4) Production of Granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] is charged with 1321.2 g of erythritol [manufactured by Nikken Chemical Co., Ltd. (Japan)], 360.0 g of low-substituted hydroxypropyl cellulose LH-32 [hydroxypropoxyl group contents of 8.8 %, manufactured by Shin-Etsu Chemical Co., Ltd. (Japan)], 18.0 g of citric acid anhydrous, and 1.8 g of aspartame, and granulation is carried out while spraying a solution which is prepared by dissolving 3.6 g of polyethylene glycol (PEG-6000) in 896.4 ml of purified water. The granules are dried to provide granulated powders. To the granulated powders are added 90.0 g of crospovidone and 5.4 g of magnesium stearate, which is admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

Hereinafter, the above "enteric coated granules having a core" is referred to as "enteric coated powders".

200.0 g of the above enteric coated powders and 300.0 g of the above mixed powders are tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 11 mm in diameter, at a tabletting pressure of 1.0 ton/cm^2 to provide tablets each weighing 500 mg.

Reference Example 1

An alkaline cellulose comprising 24.1% of NaOH, 1.7% of Na_2CO_3, 42.9% of cellulose, 31.8% of H_2O was obtained by immersing a wood pulp in 49% aqueous solution of sodium hydroxide and then by pressing it. A reactor was charged with 100 weight parts of the alkaline cellulose. Then, nitrogen gas replacement was carried out. After the replacement, 5 weight parts of propylene oxide was charged in the reactor and reacted with stirring at 40° C. for 1 hour, at 50° C. for 1 hour and at 70° C. for 1 hour to obtain 103 weight parts of a reactant.

On the other side, a kneader was charged with 2.5 weight parts of hot water at 65° C. and 0.13 weight parts of glacial acetic acid (about 40 weight % against equivalent for neutralization, initial neutralized acid) and therein, 1 weight part of the above resulting alkaline cellulose was dispersed. Then, the temperature was set at 30° C. to dissolve a part of the reactant, and 0.20 weight part of glacial acetic acid (the remainder of an equivalent for neutralization, complete neutralized acid) to obtain a processed fiber product containing a part of dissolution and a part of deposit.

The resulting product was washed with hot water at about 80° C., drained, dried, ground by means of a high rolling impact grinder, and sifted by means of a 100 mesh sieve to obtain the powder of low-substituted hydroxypropyl cellulose LH-33 (the content of hydroxypropoxyl group: 5.8 weight %, the average particle diameter: 17.8 μm).

Reference Example 2

Powders of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.7 weight %, average particle diameter: 30.8 μm) were obtained in the same manner as in Reference Example 1.

Example 2

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 300 g of Nonpareil 105 [(trade name) particle diameter: 100 to 200 μm]. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 30° C., respectively, the Nonpareil was coated by spraying a spray liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min., and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 2186 g of powders (150 to 300 μm) having a core.

Spray Liquid:

Lansoprazole	927 g
Magnesium carbonate	309 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 wt %) (average particle diameter: 17.57 μm)	154.5 g
Hydroxypropyl cellulose (Type SSL)	309 g
Purified water	3955 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 2040 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 13 g/min. to provide 2145 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	264 g
Purified water	5016 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1710 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 40° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 17 g/min., and dried for 7 minutes, and then sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 2393 g of enteric coated powders (177 to 355 μm) having a core.

Enteric Film Coating Liquid:

Eudragit L30D-55	5016.4 g
Eudragit NE30D	559.0 g
Triethyl citrate	333.7 g
Glyceryl monostearate	106.5 g
Polysorbate 80	34.8 g
Red iron oxide	1.8 g
Purified water	2547.1 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 600 g of the above enteric coated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 32° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 11 g/min., and then dried for 7 minutes to provide 617 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 334.1 μm.

Film Coating Liquid:

Mannitol	33 g
Purified water	297 g

(5) Production of Mannitol-granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp. (Japan), LAB-1] was charged with 800 g of mannitol [manufactured by Merck Japan Co., Ltd.], and granulation was carried out while spraying 315 g of purified water. The granules were dried to provide 727.3 g of granulated powders.

(6) Production of Mixed Powders

To 97.3 g of the above mannitol-granulated powders were added 105 g of the above enteric coated and mannitol coated granules having a core, 15.0 g of low-substituted hydrox-

ypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %, average particle diameter: 17.8 μm), 22.5 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 7.5 g of crospovidone, 1.5 g of citric acid anhydrous, 0.45 g of aspartame and 0.75 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(7) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 5.9 kg and 30 seconds, respectively.

Example 3

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 29° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 5654.7 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #60 circular sieve (250 μm) and a #100 circular sieve (150 μm) to provide 2424 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4608 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)) was charged with 2337.5 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 18 g/min. The spraying operation was stopped when the specified amount 6050 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 2551 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropyl methylcellulose (Type 2910, viscosity: 3 centistokes)	332.5 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %) (average particle diameter: 17.57 μm)	17.5 g
Purified water	6650 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 570 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 40° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 18 g/min. The spraying operation was stopped when the specified amount 2646 g of the enteric film coating liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes. The coated powders were sieved through a #42 circular sieve (355 μm) and a #70 circular sieve (212 μm) to provide 1116 g of enteric coated granules having a core.

The average particle diameter of the obtained granules was 326.9 μm.

Enteric Film Coating Liquid:

Eudragit L30D-55	1911 g
Eudragit NE30D	212.9 g
Triethyl citrate	127.1 g
Glyceryl monostearate	40.6 g
Polysorbate 80	13.3 g
Red iron oxide	0.8 g
Purified water	970.3 g

(4) Production of Mixed Powders

To 200 g of the above enteric coated granules having a core were added 189.7 g of mannitol, 30.0 g of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.8 weight %, average particle diameter: 17.8 μm), 60.0 g of crystalline cellulose RCEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15.0 g of crospovidone, 2.8 g of citric acid anhydrous and 25 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 4.2 kg and 24 seconds, respectively.

Example 4

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (TyDp 2)] was charged with 900 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 32° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount 5654.7 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 2280 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4608 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1020 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 15 g/min. The spraying operation was stopped when the specified amount 1980 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 1330.5 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	120 g
Titanium oxide (TiO_2)	240 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	240 g
Magnesium carbonate	120 g
Purified water	2880 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan)], MP-10 (Type 2)1 was charged with 460 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 13 g/min. The spraying operation was stopped when the specified amount 2205 of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid:

Eudragit L30D-55	2290 g
Eudragit NE30D	253 g
Triethyl citrate	153 g
Glyceryl monostearate	20 g
Polysorbate 80	8 g
Titanium oxide (TiO_2)	53 g
Sterilized Talc H (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	53 g
Purified water	2420 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 35° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 16 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex dorD. (Japan), MP-10 (Type 2)].

The spraying operation was stopped when the specified amount 824 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minute. The resulting granules were sieved through a #42 circular sieve (355 μm) and a #60 circular sieve (250 μm) to provide 806 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 326.6 μm.

Film Coating Liquid:

Mannitol	320 g
Purified water	2880 g

(5) Production of Mixed Powders

To 120 g of the above enteric coated and mannitol coated granules having a core were added 87.75 g of mannitol, 8.5 g of low-substituted hydroxypropyl cellulose LH-23 (hydroxypropoxyl group contents: 5.8 weight %), 4.5 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 19.5 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 6.5 g of crospovidone, 1.3 g of citric acid anhydrous, 1.3 g of aspartame and 0.65 g of magnesium stearate, which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

250.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch (15R), 11 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.9 kg and 20.5 seconds, respectively.

The remaining ratio of the obtained tablet after acid-resistance test was 97%.

Example 5

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 1.05 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 30° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the Specified amount 5661 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2074 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4680 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged

with 2074 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 40° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 1980 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2555 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	252 g
Titanium oxide (TiO_2)	108 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	108 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Mannitol	252 g
Purified water	3600 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1320 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance With the tangential spray method at a spray rate of 22 g/min. The specified amount 1638 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	1219.2 g
Eudragit NE30D	134.4 g
Polyethylene glycol 6000	40.8 g
Glyceryl monostearate	24.0 g
Polysorbate 80	7.2 g
Ferric oxide	0.24 g
Ferric oxide (yellow)	0.24 g
Citric acid anhydrous	0.48 g
Purified water	1693 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 76° C. and about 42° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 6552 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g

-continued

Citric acid anhydrous	0.72 g
Purified water	2624 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the above mentioned composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 819 g of the enteric film coating liquid had been sprayed.

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 35° C., respectively an f film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 882 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 1964 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 333.7 μm.

Film coating liquid:

Mannitol	180 g
Purified water	1080 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/Cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 2.6 kg and 20 seconds, respectively.

The acid-resistance of the obtained tablet was 3.5%.

Example 6

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 750 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 30° C. respectively, the Nonpareil was coated by

spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 4717. 5 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 8 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1811 g of granules having a core.

Bulk Liquid:

Lansoprazole	900 g
Magnesium carbonate	300 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	150 g
Hydroxypropyl cellulose (Type SSL)	300 g
Purified water	3900 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1811 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 38° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray imethod at a spray rate of 22 g/min. The spraying operation was stopped when the specified amount 5274 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2628 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	378 g
Titanium oxide (TiO_2)	162 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	162 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	270 g
Mannitol	378 g
Purified water	5400 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1560 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 40° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 6048 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g
Citric acid anhydrous	0.72 g
Purified water	2624 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 72° C. and about 42° C, respectively, an enteric film coating liquid (B) of the following composition preepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 819 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	609.6 g
Eudragit NE30D	68.0 g
Polyethylene glycol 6000	20.4 g
Glyceryl monostearate	12.0 g
Polysorbate 80	3.6 g
Ferric oxide	0.12 g
Ferric oxide (yellow)	0.12 g
Citric acid anhydrous	0.24 g
Purified water	846.7 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), while the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 38° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 882 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 17 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2825 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 330.5 μm.

Film Coating Liquid:

Mannitol	180 g
Purified water	1080 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KC-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 2 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.1 kg and 22 seconds, respectively.

The acid-resistance of the obtained tablet was 2.5%.

Example 7

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 750 g of Nonpareil 105 (trade name) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 30° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount 4717.5 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes to provide 1842 g of granules having a core.

Bulk Liquid:

Lansoprazole	900 g
Magnesium carbonate	300 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	150 g
Hydroxypropyl cellulose (Type SSL)	300 g
Purified water	3900 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fliudized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1842 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 74° C. and about 38° C., respectively, an undercoating liquid of the following composition prepared an advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The spraying operation was stopped when the specified amount 5365 g of the undercoatingliquid had been sprayed, and then drying was carried out in the granulator for 9 minutes. The resulting granules were sieved through a#42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 2770 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	378 g
Titanium oxide (TiO_2)	162 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	162 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	270 g
Mannitol	378 g
Purified water	5400 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1300 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 78° C. and about 39° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 5040 g of the enteric film coating liquid had been sprayed, and then drying was carried out in the granulator for 16 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2453 g of enteric coated granules having a core.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	4032 g
Eudragit NE30D	447.8 g
Triethyl citrate	269.3 g
Glyceryl monostearate	86.4 g
Polysorbate 80	25.9 g
Ferric oxide	0.86 g
Ferric oxide (yellow)	0.86 g
Citric acid anhydrous	0.72 g
Purified water	2624 g

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1000 g of the above enteric coated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 38° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 19 g/min. The specified amount 273 g of the enteric film coating liquid had, been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	610.4 g
Eudragit NE30D	68.0 g
Polyethylene glycol 6000	20.4 g
Glyceryl monostearate	12.0 g
Polysorbate 80	3.6 g
Ferric oxide	0.12 g
Ferric oxide (yellow)	0.12 g
Citric acid anhydrous	0.24 g
Purified water	845.12 g

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), while the inlet air temperature and the temperature of the loading being controlled at 75° C. and about 35° C., respectively, an film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 20 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 294 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 1061 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules was 307.1 μm.

Film Coating Liquid:

Mannitol	120 g
Purified water	720 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 207 g of mannitol, 30 g

of low-substituted hydroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of crospovidone, 3 g of citric acid anhydrous, 9 g of aspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 13 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.2 kg and 24 seconds, respectively.

Example 8

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 900 g of Nonpareil 105T (trade name) (particle diameter of 100 to 200 m). With the inlet air temperature and the temperature of the loading being controlled at 71 to 78° C. and about 31° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 5550 g of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 21 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1723 g of granules having a core.

Bulk Liquid:

Lansoprazole	1080 g
Magnesium carbonate	360 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Hydroxypropyl cellulose (Type SSL)	360 g
Purified water	4680 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluided coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 2074 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 77° C. and about 41° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The spraying operation was stopped when the specified amount 2787 g of the undercoating liquid had been sprayed, and then drying was carried out in the granulator for 13 minutes. The resulting granules were sieved through a #42 circular sieve (350 μm) and a #100 circular sieve (150 μm) to provide 1958 g of film-undercoated granules having a core.

Undercoating Liquid:

Hydroxypropylmethylcellulose (Type 2910, viscosity: 3 centistokes)	252 g
Titanium oxide (TiO_2)	108 g
Sterilized Talc (trade name) [produced by Matsumura Sangyo Co. Ltd. (Japan)]	108 g
Low-substituted hydroxypropyl cellulose LH-32 (hydroxypropoxyl group contents: 8.8 weight %)	180 g
Mannitol	252 g
Purified water	3600 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized Goating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 1100 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 41° C., respectively, an enteric film coating liquid (A) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 1365 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (A):

Eudragit L30D-55	1017.3 g
Eudragit NE30D	113.3 g
Polyethylene glycol 6000	34.0 g
Glyceryl monostearate	20.0 g
Polysorbate 80	6.0 g
Ferric oxide	0.2 g
Ferric oxide (yellow)	0.2 g
Citric acid anhydrous	0.4 g
Purified water	1410.8 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 76° C. and about 41° C., respectively, an enteric film coating liquid (B) of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. The specified amount 5040 g of the enteric film coating liquid had been sprayed.

Enteric Film Coating Liquid (B):

Eudragit L30D-55	3360 g
Eudragit NE30D	373.2 g
Triethyl citrate	224.4 g
Glyceryl monostearate	72.0 g
Polysorbate 80	21.6 g
Ferric oxide	0.72 g
Ferric oxide (yellow)	0.72 g
Citric acid anhydrous	0.6 g
Purified water	1706.8 g

Following this, with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 42° C., respectively, an enteric film coating liquid (A) of the above mentioned composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 21 g/min. The specified amount 682.5 g of the enteric film coating liquid had been sprayed.

(4) Production of Enteric Coated and Mannitol Coated Granules Having a Core

Following (3), with the inlet air temperature and the temperature of the loading being controlled at 80° C. and about 36° C., respectively, an film coating liquid of the

following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 22 g/min. using a centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)]. The spraying operation was stopped when the specified amount 735 g of the film coating liquid had been sprayed, and then drying was carried out in the granulator for 10 minutes. The resulting granules were sieved through a #35 circular sieve (420 μm) and a #60 circular sieve (250 μm) to provide 2319.5 g of enteric coated and mannitol coated granules having a core.

The average particle diameter of the obtained granules; was 392.7 μm.

Film Coating Liquid:

Mannitol	100 g
Purified water	600 g

(5) Production of Mixed Powders

To 270 g of the above enteric coated and mannitol coated granules having a core were added 204.0 g of mannitol, 30 g of low-substituted hyaroxypropyl cellulose LH-33 (hydroxypropoxyl group contents: 5.8 weight %), 30 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Co., Ltd. (Japan)], 15 g of [crospovidone, 3 g of citric acid anhyaroug, 9 g of dspartame, 6 g of magnesium stearate and 3 g of flavor [STRAWBERRY DURAROME (trade name), manufactured by Nihon Filmenich Co., Ltd. (Japan)], which was admixed in a bag to give mixed powders.

(6) Production of Orally Disintegrable Tablets

570 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 12 mm in diameter, at a tabletting pressure of 1.5 ton/cm^2, to provide tablets each weighing 570 mg.

The hardness and oral disintegration time of each tablet thus obtained were 3.7 kg and 35 seconds, respectively.

The acid-resistance of the obtained tablet was 3.4%.

Example 9

(1) Production of Granules Having a Core

A centrifugal fluidized coating granulator (manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 300 g of Nonpareil 105 (70–140) (particle diameter of 100 to 200 μm). With the inlet air temperature and the temperature of the loading being controlled at 85° C. and about 28° C. respectively, the Nonpareil was coated by spraying a bulk liquid of the following composition prepared in advance in accordance with the tangential spray method at a spray rate of 20 g/min. The spraying operation was stopped when the specified amount of the bulk liquid had been sprayed, and then drying was carried out in the granulator for 7 minutes. The resulting granules were sieved through a #48 circular sieve (300 μm) and a #100 circular sieve (150 μm) to provide 757 g of granules having a core.

Bulk Liquid:

Lansoprazole	300 g
Magnesium carbonate	100 g
L-HPC	50 g
HPC (Type SSL)	100 g
Water	1650 g

(2) Production of Film-undercoated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 680 g of the above granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 70° C. and about 36° C., respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a spray rate of 10 g/min. to provide 672 g of film-undercoated granules having a core.

Undercoating Liquid:

HPMC (Type 2910, viscosity: 3 centistokes)	32 g
Talc	8 g
Water	760 g

(3) Production of Enteric Coated Granules Having a Core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp. (Japan), MP-10 (Type 2)] was charged with 450 g of the above film-undercoated granules having a core. With the inlet air temperature and the temperature of the loading being controlled at 65° C. and about 36° C., respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at a sprayer rate of 17 g/min. The Coated powders were dried in vacuum at 40° C. for 16 hours, and sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 950 g of enteric coated granules having a core.

The average particle diameter of the obtained granules was 285.4 μm.

Enteric Film Coating Liquid:

Eudragit L30D-55	1078.3 g
Eudragit NE30D	138.5 g
Triethyl citrate	46.0 g
Glyceryl monostearate	16.5 g
Talc	16.0 g
Polysorbate 80	9.0 g
Iron oxide	0.5 g
Water	2038.5 g

Sieve	weight ratio
#18 (850 μm) on	0%
#30 (500 μm) on	0%
#200 (75 μm) on	100%
#200 (75 μm) pass	0%

(4) Production of Granulated Powders

A fluidized bed granulator [manufactured by Powrex Corp., (Japan), LAB-1] was charged with 1321.2 g of erythritol [manufactured by Nikken Chemical Co., Ltd. (Japan)], 360.0 g of low-substituted hydroxypropyl cellulose LH-32 [hydroxypropoxyl group contents of 8.8%, manufactured by Shin-PteU Chemical Co., Ltd. (Japan)], 18.0 g of citric acid anhydrous, and 1.8 g of aspartame, and granulation was carried out while spraying a solution which was prepared by dissolving 3.6 g of polyethylene glycol (PEG-6000) in 896.4 ml of purified water. The granules were dried

to provide granulated powders. To the granulated powders were added 90.0 g of crospovidone and 5.4 a of magnesium stearate, which was admixed in a bag to give mixed powders.

(5) Production of Orally Disintegrable Tablets

200.0 g of the above enteric coated granules having a core and 300.0 g of the above mixed powders were tabletted using Autograph (trade name; compressing force measurement apparatus) with a punch having a beveled edge, 11 mm in diameter, at a tabletting pressure of 1.0 ton/cm^2, to provide tablets each weighing 500 mg.

The hardness, the oral disintegration time and remaining ratio after acid-resistance test of each tablet thus obtained were 4.2 kg, 27 seconds and 96.3%, respectively.

INDUSTRIAL APPLICABILITY

The orally disintegrable tablet of the present invention has superior disintegrability or dissolution so that it can be used for treatment or prevention of various diseases, as an orally disintegrable tablet capable of being administered to the aged of children and easily administered without water. Also, because the orally disintegrable tablet of the present invention contains fine granules having the average particle diameter and an enteric coating layer such that it will not impart roughness in mouth, it can be administered easily without discomfort at the administration and has superior acid-resistance.

Further, because the orally disintegrable tablet of the present invention has a suitable strength such that it will not be substantially damaged through production processes or circulation processes, it is superior in stability for long-term storage and easy of use at the administration.

Further, because the fine granule of the present invention is characterized in that it stably retains the acid-labile physiologically active substance, contains the physiologically active substance in high content, be small and has superior stability, it can be used for producing various compact pharmaceutical preparations such as tablets, capsules, suspensions and so forth. Such preparations are easy of use at the administration. In addition, the fine granule of the present invention has superior acid-resistance after compression.

What is claimed is:

1. An orally disintegrable tablet which comprises

(i) fine granules having an average particle diameter of 400 μm or less, which fine granules comprise a composition coated by an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent, said composition having 10 weight % or more of an acid-labile physiologically active substrate that is lansoprazole and (ii) an additive wherein said tablet having a hardness strength of about 1 to about 20 kg, is orally disintegrable.

2. An orally disintegrable tablet of claim **1**, wherein the average particle diameter of the fine granule is 300 to 400 μm.

3. An orally disintegrable tablet of claim **1**, wherein the fine granules further comprise a basic inorganic salt.

4. An orally disintegrable tablet of claim **1**, wherein the additive comprises a water-soluble sugar alcohol.

5. An orally disintegrable tablet of claim **1**, wherein the composition coated by an enteric coating layer is further coated by a coating layer which comprises a water-soluble sugar alcohol.

6. An orally disintegrable tablet of claim **4**, wherein the additive comprises (1) crystalline cellulose and/or (ii) low-substituted hydroxypropyl cellulose.

7. An orally disintegrable tablet of claim **1**, wherein the particle diameter of the fine granules is practically 425 μm or less.

8. An orally disintegrable tablet of claim **1**, wherein the particle diameter of the fine granules is practically 400 μm or less.

9. An orally disintegrable tablet of claim **3**, wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium.

10. An orally disintegrable tablet of claim **1**, wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose.

11. An orally disintegrable tablet of claim **10**, wherein the core comprises 50 weight % or more of lactose.

12. An orally disintegrable tablet of claim **10**, wherein the core comprises 40 to 50 weight % of crystalline cellulose and 50 to 60 weight % of lactose.

13. An orally disintegrable tablet of claim **1**, wherein the composition comprises 20 weight % or more of an acid-labile physiologically active substance.

14. An orally disintegrable tablet of claim **1**, wherein the composition comprises 20 to 50 weight % of an acid-labile physiologically active substance.

15. An orally disintegrable tablet of claim **1**, wherein the fine granules are produced by fluidized-bed granulation method.

16. An orally disintegrable tablet of claim **1**, wherein the enteric coating layer comprises an aqueous enteric polymer agent.

17. An orally disintegrable tablet of claim **16**, wherein the aqueous enteric polymer agent is a methacrylate copolymer.

18. An orally disintegrable tablet of claim **1**, wherein the sustained-release agent is a methacrylate copolymer.

19. An orally disintegrable tablet of claim **16**, wherein the sustained-release agent is in an amount of 5 15 weight % relative to 100 weight % of the aqueous enteric polymer agent.

20. An orally disintegrable tablet of claim **4**, wherein the water-soluble sugar alcohol is erythritol.

21. An orally disintegrable tablet of claim **4**, wherein the water-soluble sugar alcohol si mannitol.

22. An orally disintegrable tablet of claim **5**, wherein the water-soluble sugar alcohol is in an amount of 5 to 97 weight % relative to 100 weight % of the orally disintegrable tablet apart from the fine granules.

23. An orally disintegrable tablet of claim **4**, wherein the crystalline cellulose is in an amount of 3 to 50 weight % relative to 100 weight % of the tablet apart from the fine granule.

24. An orally disentegrable tablet of claim **6**, wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropyl cellulose is 7.0 to 9.9 weight %.

25. An orally disintegrable tablet of claim **6**, wherein the content of hydroxypropoxyl group in the low-substituted hydroxypropoxyl cellulose is 5.0 7.0 weight %.

26. An orally disintegrable tablet of claim **1**, which further comprises crosprovidone.

27. An orally disintegrable tablet of claim **1**, wherein the oral disintegration time is one minute or less.

28. An orally disintegrable tablet of claim **1**, which comprises no lubricant inside the tablet.

29. Fine granules having an average particle diameter of 400 μm or less, which comprise a composition coated by an enteric coating layer comprising a first component which is an enteric coating agent and a second component which is a sustained-release agent, said composition having (i) 25

weight % or more of an acid-liable physiologically active substance that is lansoprazole and (ii) a basic inorganic salt.

30. Fine granules of claim **28**, wherein the average particle diameter of the fine granules is 300 to 400 μm.

31. Fine granules of claim **28**, wherein the particle diameter of the fine granules is practically 425 μm or less.

32. Fine granules of claim **28**, wherein the particle diameter of the fine granules is practically 400 μm or less.

33. Fine granules of claim **28**, wherein the basic inorganic salt is a salt of magnesium and/or a salt of calcium.

34. Fine granules of claim **28**, wherein the composition comprises a core being coated by a benzimidazole compound and a basic inorganic salt, said core comprising crystalline cellulose and lactose.

35. Fine granules of claim **34**, wherein the core comprises 50 weight % or more of lactose.

36. Fine granules of claim **28**, wherein the composition comprises 25 to 40 weight % of an acid-labile physiologically active substance.

37. Fine granules of claim **28**, which are produced by fluidized-bed granulation method.

38. Fine granules of claim **28**, wherein the enteric coating layer comprises an aqueous enteric polymer agent.

39. Fine granules of claim **38**, wherein the aqueous enteric polymer agent is a methacrylate copolymer.

40. Fine granules of claim **28**, wherien the sustained-release agent is a methacrylate copolymer.

41. Fine granules of claim **28**, wherein the sustained-release agent is in an amount of 5 to 15 weight % relative to 100 weight % of the aqueous enteric polymer agent.

42. Fine granules of claim **28**, wherein the enteric coating layer is in an amount of 50 to 70 weight % relative to 100 weight % of the fine granules.

43. A tablet, granule, fine granule, capsule, effervescent or suspension preparation which comprises the fine granules of claim **28**.

44. An orally disintegrable tablet of claim **16**, wherein the sustained-release agent is in an amount of 5 to 30 weight % relative to 100 weight % of the aqueous enteric polymer agent.

45. Fine granules of claim **38**, wherein the sustained-release agent is in an amount of 5 to 30% relative to 100 weight % of the aqueous enteric polymer agent.

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JS 44 (Rev. 11/04)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
TAKEDA PHARMACEUTICAL COMPANY LIMITED and TAP PHARMACEUTICAL PRODUCTS INC.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)
Rodger D. Smith II, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, 1201 North Market Street, P.O. Box 1347, Wilmington, DE 19899-1347, (302) 658-9200

DEFENDANTS
BARR PHARMACEUTICALS, INC. and BARR LABORATORIES, INC.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**:
Suit for patent infringement under 35 U.S.C. Section 271
Brief description of cause:

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 **DEMAND $** CHECK YES only if demanded in complaint: **JURY DEMAND:** ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE Robinson DOCKET NUMBER 07-331

DATE June 9, 2008 SIGNATURE OF ATTORNEY OF RECORD

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RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____